PCT/EP2004/014490

17 12 2004

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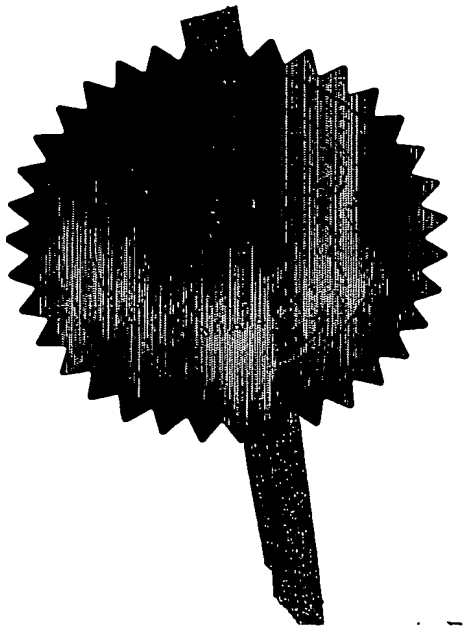

Signed Stephen Hordley

Dated 23 November 2004

Patents Form 1/77

Patents Act 1977
(Rule 16)

16 MAR 2004

The Patent Office

1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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NP10 8QQ

17MAR04 E881481-2 D02029
P01/7700 0.00-0405936.6 NONE

1. Your Reference — **APB/PB60739P**

2. Patent application number *(The Patent office will fill in this part)* — 0405936.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number *(if you know it)* — 00473587003

If the applicant is a corporate body, give the country/state of its corporation — **GB**

4 Title of the invention — **COMPOUNDS**

5 Name of your agent *(if you have one)* — **ANTHONY P BREEN**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY
980 GREAT WEST ROAD
BRENTFORD, MIDDLESEX
TW8 9GS, GB

Patents ADP number *(if you know it)* — 08072555004

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. Divisionals: etc Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing (day / month / year)

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — **YES**

Answer YES if:

a). any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body

Otherwise answer NO See note (d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheet of this form	0
Description	188
Claim(s)	0
Abstract	0
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

A C CONNELL

Signature(s) A C Connell **Date: 16 March 2004**

12. Name and daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom **LESLEY WELLS 01 438 768599**

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form

d) If you have answered "Yes" in part 8, a Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

COMPOUNDS

The present invention relates to pyrazolo[3,4-b]pyridine compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the pyrazolo[3,4-b]pyridine compounds in therapy, for example as inhibitors of phosphodiesterase type IV (PDE4) and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis.

Background to the Invention

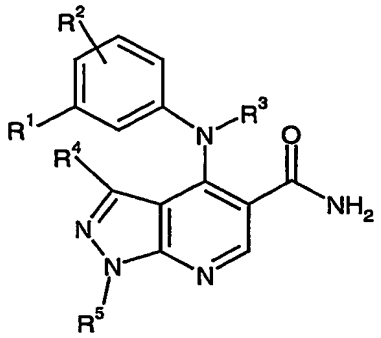
US 3,979,399, US 3,840,546, and US 3,966,746 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxamides wherein the 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 3-6-membered heterocyclic group such as pyrrolidino, piperidino and piperazino. The compounds are disclosed as central nervous system depressants useful as ataractic, analgesic and hypotensive agents.

US 3,925,388, US 3,856,799, US 3,833,594 and US 3,755,340 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxylic acids and esters. The 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 5-6-membered heterocyclic group in which an additional nitrogen is present such as pyrrolidino, piperidino, pyrazolyl, pyrimidinyl, pyridazinyl or piperazinyl. The compounds are mentioned as being central nervous system depressants useful as ataractic agents or tranquilisers, as having antiinflammatory and analgesic properties. The compounds are mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

H. Hoehn et al., *J. Heterocycl. Chem.*, 1972, 9(2), 235-253 discloses a series of 1*H*-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives with 4-hydroxy, 4-chloro, 4-alkoxy, 4-hydrazino, and 4-amino substituents.

CA 1003419, CH 553 799 and T.Denzel, *Archiv der Pharmazie*, 1974, 307(3), 177-186 disclose 4,5-disubstituted 1*H*-pyrazolo[3,4-b]pyridines unsubstituted at the 1-position.

Japanese laid-open patent application JP-2002-20386-A (Ono Yakuhin Kogyo KK) published on 23 January 2002 discloses pyrazolopyridine compounds of the following formula:



JP-2002-20386-A
(Ono)

wherein R^1 denotes 1) a group $-OR^6$, 2) a group $-SR^7$, 3) a C2-8 alkynyl group, 4) a nitro group, 5) a cyano group, 6) a C1-8 alkyl group substituted by a hydroxy group or a C1-8 alkoxy group, 7) a phenyl group, 8) a group $-C(O)R^8$, 9) a group $-SO_2NR^9R^{10}$, 10) a group $-NR^{11}SO_2R^{12}$, 11) a group $-NR^{13}C(O)R^{14}$ or 12) a group $-CH=NR^{15}$. R^6 and R^7 denote i) a hydrogen atom, ii) a C1-8 alkyl group, iii) a C1-8 alkyl group substituted by a C1-8 alkoxy group, iv) a trihalomethyl group, v) a C3-7 cycloalkyl group, vi) a C1-8 alkyl group substituted by a phenyl group or vii) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^2 denotes 1) a hydrogen atom or 2) a C1-8 alkoxy group. R^3 denotes 1) a hydrogen atom or 2) a C1-8 alkyl group. R^4 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group which may be substituted by 1-3 halogen atoms or 6) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^5 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group or 5) a phenyl group which may be substituted by 1-3 substituents. In group R^3, a hydrogen atom is preferred. In group R^4, methyl, ethyl, cyclopropyl, cyclobutyl or cyclopentyl are preferred. The compounds of JP-2002-20386-A are stated as having PDE4 inhibitory activity and as being useful in the prevention and/or treatment of inflammatory diseases and many other diseases.

1,3-Dimethyl-4-(arylamino)-pyrazolo[3,4-b]pyridines with a 5-$C(O)NH_2$ substituent similar or identical to those in JP-2002-20386-A were disclosed as orally active PDE4 inhibitors by authors from Ono Pharmaceutical Co. in: H. Ochiai et al., *Bioorg. Med. Chem. Lett.*, 5th January 2004 issue, vol. 14(1), pp. 29-32 (available on or before 4th December 2003 from the Web version of the journal: "articles in press").

EP 0 076 035 A1 (ICI Americas) discloses pyrazolo[3,4-b]pyridine derivatives as central nervous system depressants useful as tranquilisers or ataractic agents for the relief of anxiety and tension states.

The compound cartazolate, ethyl 4-(n-butylamino)-1-ethyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylate, is known. J.W. Daly et al., *Med. Chem. Res.*, 1994, 4, 293-306 and D. Shi et al., *Drug Development Research*, 1997, 42, 41-56 disclose a series of 4-

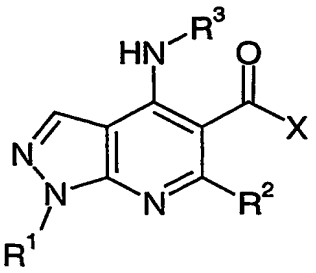
(amino)substituted 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives, including ethyl 4-cyclopentylamino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate, and their affinities and antagonist activities at A_1- and A_{2A}-adenosine receptors, and the latter paper discloses their affinities at various binding sites of the $GABA_A$-receptor channel.

S. Schenone et al., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2529-2531, and F. Bondavalli et al., *J. Med. Chem.*, 2002, vol. 45 (Issue 22, 24 October 2002, allegedly published on Web 09/24/2002), pp. 4875-4887 disclose a series of 4-amino-1-(2-chloro-2-phenylethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl esters as A_1-adenosine receptor ligands.

WO 02/060900 A2 appears to disclose, as MCP-1 antagonists for treatment of allergic, inflammatory or autoimmune disorders or diseases, a series of bicyclic heterocyclic compounds with a $-C(O)-NR^4-C(O)-NR^5R^6$ substituent, including isoxazolo[5,4-b]pyridines and 1*H*-pyrazolo[3,4-b]pyridines (named as pyrazolo[5,4-b]pyridines) with the $-C(O)-NR^4-C(O)-NR^5R^6$ group as the 5-substituent and optionally substituted at the 1-, 3-, 4-, and/or 6-positions. Bicyclic heterocyclic compounds with a $-C(O)NH_2$ substituent instead of the $-C(O)-NR^4-C(O)-NR^5R^6$ substituent are alleged to be disclosed in WO 02/060900 as intermediates in the synthesis of the $-C(O)-NR^4-C(O)-NR^5R^6$ substituted compounds.

WO 00/15222 (Bristol-Myers Squibb) discloses *inter alia* pyrazolo[3,4-b]pyridines having *inter alia* a $C(O)-X_1$ group at the 5-position and a group E_1 at the 4-position of the ring system. Amongst other things, X_1 can for example be $-OR_9$, $-N(R_9)(R_{10})$ or $-N(R_5)(-A_2-R_2)$, and E_1 can for example be $-NH-A_1$-cycloalkyl, $-NH-A_1$-substituted cycloalkyl, or $-NH-A_1$-heterocyclo; wherein A_1 is an alkylene or substituted alkylene bridge of 1 to 10 carbons and A_2 can for example be a direct bond or an alkylene or substituted alkylene bridge of 1 to 10 carbons. The compounds are disclosed as being useful as inhibitors of cGMP phosphodiesterase, especially PDE type V, and in the treatment of various cGMP-associated conditions such as erectile dysfunction. Compounds with a cycloalkyl or heterocyclo group directly attached to -NH- at the 4-position of the pyrazolo[3,4-b]pyridine ring system and/or having PDE4 inhibitory activity do not appear to be disclosed in WO 00/15222.

Copending unpublished patent application PCT/EP03/11814, filed on 12 September 2003 in the name of Glaxo Group Limited, and incorporated herein by reference, discloses pyrazolo[3,4-b]pyridine compounds or salts thereof with a $4-NHR^3$ group and a 5-C(O)-X group, according to this formula (I):



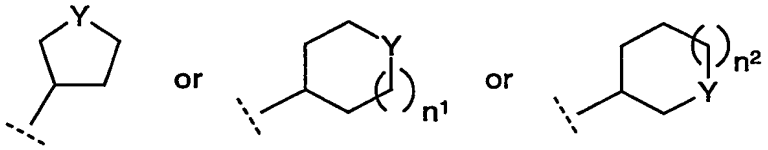
(I)

wherein:

R^1 is C_{1-4}alkyl, C_{1-3}fluoroalkyl, $-CH_2CH_2OH$ or $-CH_2CH_2CO_2C_{1-2}$alkyl;

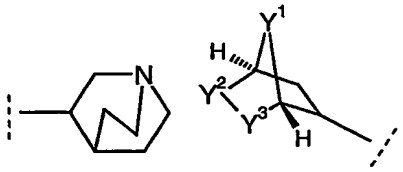
R^2 is a hydrogen atom (H), methyl or C_1fluoroalkyl;

R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc);



(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and in which Y is O, S, SO_2, or NR^{10};



(dd) (ee)

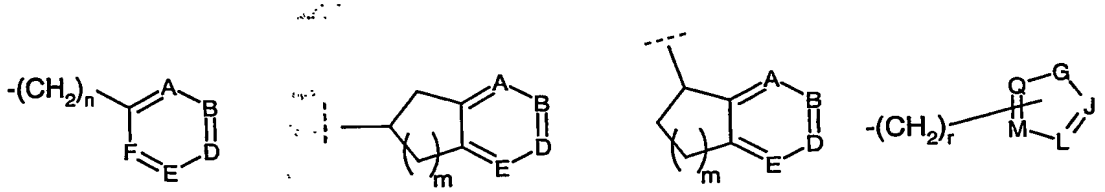
or R^3 is a bicyclic group (dd) or (ee): ;

and wherein X is NR^4R^5 or OR^{5a}.

In PCT/EP03/11814, R^4 is a hydrogen atom (H); C_{1-6}alkyl; C_{1-3}fluoroalkyl; or C_{2-6}alkyl substituted by one substituent R^{11}.

In PCT/EP03/11814, R^5 can be: a hydrogen atom (H); C_{1-8}alkyl; C_{1-8} fluoroalkyl; C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group; $-(CH_2)_n{}^4-C_{3-8}$cycloalkyl optionally substituted, in the $-(CH_2)_n{}^4-$ moiety or in the C_{3-8}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^4 is 1, 2 or 3; C_{2-6}alkyl substituted by one or two independent substituents R^{11}; $-(CH_2)_n{}^{11}-C(O)R^{16}$; $-(CH_2)_n{}^{12}-C(O)NR^{12}R^{13}$; $-CHR^{19}-C(O)NR^{12}R^{13}$; $-(CH_2)_n{}^{12}-C(O)OR^{16}$; $-(CH_2)_n{}^{12}-C(O)OH$; $-CHR^{19}-C(O)OR^{16}$; $-CHR^{19}-C(O)OH$; $-(CH_2)_n{}^{12}-SO_2-NR^{12}R^{13}$; $-(CH_2)_n{}^{12}-SO_2R^{16}$; or $-(CH_2)_n{}^{12}-CN$; $-(CH_2)_n{}^{13}$-Het; or optionally substituted phenyl.

Alternatively, in PCT/EP03/11814, R^5 can have the sub-formula (x), (y), (y1) or (z):



(x) (y) (y1) (z)

wherein in sub-formula (x), n = 0, 1 or 2; in sub-formula (y) and (y1), m = 1 or 2; and in sub-formula (z), r = 0, 1 or 2; and wherein in sub-formula (x) and (y) and (y1), none, one or two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-) provided that no more than one of A, B, D, E and F is nitrogen-oxide, and the remaining of A, B, D, E and F are independently CH or CR^6; and provided that when n is 0 in sub-formula (x) then one or two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-) and no more than one of A, B, D, E and F is nitrogen-oxide;

In PCT/EP03/11814, each R^6, independently of any other R^6 present, is: a halogen atom; C_{1-6}alkyl; C_{1-4}fluoroalkyl; C_{1-4}alkoxy; C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; $-C(O)R^{16a}$; $-C(O)OR^{30}$; $-S(O)_2-R^{16a}$; $R^{16a}-S(O)_2-NR^{15a}-$; $R^7R^8N-S(O)_2-$; C_{1-2}alkyl-$C(O)-R^{15a}N-S(O)_2-$; C_{1-4}alkyl-$S(O)-$; Ph-$S(O)-$; R^7R^8N-CO-; $-NR^{15}-C(O)R^{16}$; R^7R^8N; OH; C_{1-4}alkoxymethyl; C_{1-4}alkoxyethyl; C_{1-2}alkyl-$S(O)_2-CH_2-$; $R^7R^8N-S(O)_2-CH_2-$; C_{1-2}alkyl-$S(O)_2-NR^{15a}-CH_2-$; $-CH_2-OH$; $-CH_2CH_2-OH$; $-CH_2-NR^7R^8$; $-CH_2-CH_2-NR^7R^8$; $-CH_2-C(O)OR^{30}$; $-CH_2-C(O)-NR^7R^8$; $-CH_2-NR^{15a}-C(O)-C_{1-3}$alkyl; $-(CH_2)_n{}^{14}$-Het^1 where n^{14} is 0 or 1; cyano (CN); Ar^{5b}; or phenyl, pyridinyl or pyrimidinyl wherein the phenyl, pyridinyl or pyrimidinyl independently are optionally substituted by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or two adjacent R^6 taken together can be $-O-(CMe_2)-O-$ or $-O-(CH_2)_n{}^{14}-O-$ where n^{14} is 1 or 2.

In PCT/EP03/11814, in sub-formula (z), G is O or S or NR^9 wherein R^9 is a hydrogen atom (H), C_{1-4}alkyl or C_{1-4}fluoroalkyl; none, one, two or three of J, L, M and Q are nitrogen; and the remaining of J, L, M and Q are independently CH or CR^6 where R^6, independently of any other R^6 present, is as defined therein.

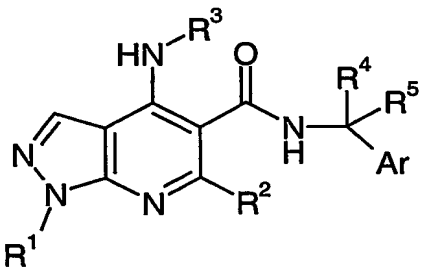
The pyrazolo[3,4-b]pyridine compounds of formula (I) and salts thereof disclosed in PCT/EP03/11814 are disclosed as being inhibitors of phosphodiesterase type IV (PDE4), and as being useful for the treatment and/or prophylaxis of an inflammatory and/or

allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis, or allergic rhinitis.

The Invention

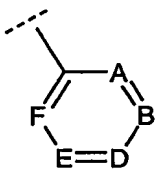
We have now found new pyrazolo[3,4-b]pyridine compounds, having a -C(O)-NH-C(R^4)(R^5)-aryl substituent at the 5-position of the pyrazolo[3,4-b]pyridine ring system wherein at least one of R^4 and R^5 is not a hydrogen atom (H), which compounds inhibit phosphodiesterase type IV (PDE4).

The present invention therefore provides a compound of formula (I) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):

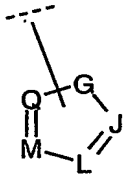


(I)

wherein Ar has the sub-formula (x) or (z):



(x)



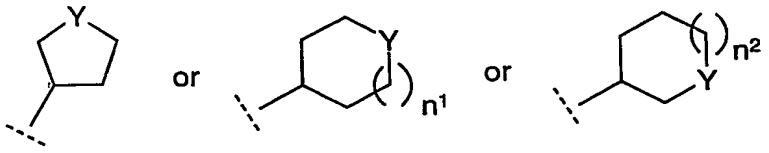
(z)

and wherein:

R^1 is C_{1-4}alkyl, C_{1-3}fluoroalkyl, or -CH_2CH_2OH;

R^2 is a hydrogen atom (H), methyl or C_1fluoroalkyl;

R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc);

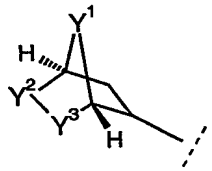


(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and in which Y is O, S, SO_2, or NR^{10}; where R^{10} is a hydrogen atom (H), C_{1-2}alkyl, C_{1-2}fluoroalkyl, $CH_2C(O)NH_2$, $C(O)NH_2$, C(O)NHMe, C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_{1-2}alkyl;

and wherein in R^3 the C_{3-8}cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted on a ring carbon with one or two substituents independently being oxo (=O); OH; C_{1-2}alkoxy; C_{1-2}fluoroalkoxy; NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-4} straight-chain alkyl; C_{1-2}alkyl; C_{1-2}fluoroalkyl; -CH_2OH; -CH_2CH_2OH; -CH_2NHR^{22} wherein R^{22} is H or C_{1-2}alkyl; -$C(O)OR^{23}$ wherein R^{23} is H or C_{1-2}alkyl; -$C(O)NHR^{24}$ wherein R^{24} is H or C_{1-2}alkyl; -$C(O)R^{25}$ wherein R^{25} is C_{1-2}alkyl; fluoro; hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-4}alkyl); and wherein any OH, alkoxy, fluoroalkoxy or NHR^{21} substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc);

and wherein, when R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, then the cycloalkenyl is optionally substituted with one substituent being fluoro or C_{1-2}alkyl or two substituents independently being fluoro or methyl , and the R^3 ring carbon bonded to the -NH- group of formula (I) does not partake in the cycloalkenyl double bond;



or R^3 is a bicyclic group of sub-formula (ee): (ee) wherein Y^1, Y^2 and Y^3 independently are CH_2 or oxygen (O) provided that no more than one of Y^1, Y^2 and Y^3 is oxygen (O);

and wherein:

R^4 is a hydrogen atom (H), methyl, ethyl, n-propyl, isopropyl, C_{1-2}fluoroalkyl, cyclopropyl, $-CH_2OR^{4a}$, $-CH(Me)OR^{4a}$, or $-CH_2CH_2OR^{4a}$, wherein R^{4a} is a hydrogen atom (H), methyl (Me), or C_1fluoroalkyl such as CF_3 or CHF_2; and

R^5 is a hydrogen atom (H); C_{1-8}alkyl (e.g. C_{1-6}alkyl or C_{1-4}alkyl); C_{1-3}fluoroalkyl; C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group; or $-(CH_2)_n{}^4$-C_{3-8}cycloalkyl optionally substituted, in the $-(CH_2)_n{}^4$- moiety or in the C_{3-8}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^4 is 1 or 2;

or R^5 is C_{1-4}alkyl substituted by one substituent R^{11}; wherein R^{11} is: hydroxy (OH); C_{1-6}alkoxy; C_{1-2}fluoroalkoxy; phenyloxy; (monofluoro- or difluoro-phenyl)oxy; (monomethyl- or dimethyl-phenyl)oxy; benzyloxy; $-NR^{12}R^{13}$; $-NR^{15}$-C(O)R^{16}; $-NR^{15}$-C(O)-NH-R^{15}; or $-NR^{15}$-$S(O)_2R^{16}$;

or R^5 is C_{2-4}alkyl substituted on different carbon atoms by two hydroxy (OH) substituents;

or R^5 is $-(CH_2)_n{}^{11}$-C(O)R^{16}; $-(CH_2)_n{}^{11}$-C(O)$NR^{12}R^{13}$; $-CHR^{19}$-C(O)$NR^{12}R^{13}$; $-(CH_2)_n{}^{11}$-C(O)OR^{16}; $-(CH_2)_n{}^{11}$-C(O)OH; $-CHR^{19}$-C(O)OR^{16}; $-CHR^{19}$-C(O)OH; $-(CH_2)_n{}^{11}$-$S(O)_2$-$NR^{12}R^{13}$; $-(CH_2)_n{}^{11}$-$S(O)_2R^{16}$; or $-(CH_2)_n{}^{11}$-CN; wherein n^{11} is 0, 1, 2 or 3 (wherein for each R^5 group n^{11} is independent of the value of n^{11} in other R^5 groups); and wherein R^{19} is C_{1-2}alkyl;

or R^5 is $-(CH_2)_n{}^{13}$-Het, wherein n^{13} is 0, 1 or 2 and Het is a 4-, 5-, 6- or 7-membered saturated or unsaturated heterocyclic ring, other than $-NR^{12}R^{13}$, containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-hetero-atoms present are not bound to the $-(CH_2)_n{}^{13}$- moiety when n^{13} is 0; wherein any ring-nitrogens which are present and which are not unsaturated (i.e. which do not partake in a double bond) and which are not connecting nitrogens (i.e. which are not nitrogens bound to the $-(CH_2)_n{}^{13}$- moiety or to the carbon atom to which R^5 is attached) are present as NR^{17}; and wherein one or two of the carbon ring-atoms are independently optionally substituted by C_{1-2}alkyl;

or R^5 is phenyl (Ph), $-CH_2$-Ph, -CHMe-Ph, -CHEt-Ph, CMe_2Ph, or $-CH_2CH_2$-Ph, wherein the phenyl ring Ph is optionally substituted with one or two substituents independently being: a halogen atom; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-2}fluoroalkyl (e.g. trifluoromethyl); C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy (e.g. trifluoromethoxy

or difluoromethoxy); cyclopropyl; cyclopropyloxy; -C(O)-C_{1-4}alkyl; -C(O)OH; -C(O)-OC_{1-4}alkyl; C_{1-4}alkyl-S(O)$_2$-; C_{1-4}alkyl-S(O)$_2$-NR^{8a}-; $R^{7a}R^{8a}N$-S(O)$_2$-; $R^{7a}R^{8a}N$-C(O)-; -NR^{8a}-C(O)-C_{1-4}alkyl; $R^{7a}R^{8a}N$; OH; nitro (-NO_2); or cyano (-CN);

or R^4 and R^5 taken together are –$(CH_2)_p{}^1$– or -$(CH_2)_p{}^3$-X^5-$(CH_2)_p{}^4$-, in which: X^5 is O or NR^{17a}; p^1 = 2, 3, 4, 5 or 6, and p^3 and p^4 independently are 1, 2 or 3 provided that if p^3 is 3 then p^4 is 1 or 2 and if p^4 is 3 then p^3 is 1 or 2;

provided that at least one of R^4 and R^5 is not a hydrogen atom (H);

and wherein, in sub-formula (x):

A is C-R^{6A}, nitrogen (N) or nitrogen-oxide (N^+-O^-),
B is C-R^{6B}, nitrogen (N) or nitrogen-oxide (N^+-O^-),
D is C-R^{6D}, nitrogen (N) or nitrogen-oxide (N^+-O^-),
E is C-R^{6E}, nitrogen (N) or nitrogen-oxide (N^+-O^-),
F is C-R^{6F}, nitrogen (N) or nitrogen-oxide (N^+-O^-),

wherein, R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} independently are: a hydrogen atom (H), a halogen atom; C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl); C_{1-4}fluoroalkyl (e.g. C_{1-2}fluoroalkyl); C_{3-6}cycloalkyl; C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; -C(O)R^{16a}; -C(O)OR^{30}; -S(O)$_2$-R^{16a} (e.g. C_{1-2}alkyl-S(O)$_2$-); R^{16a}-S(O)$_2$-NR^{15a}- (e.g. C_{1-2}alkyl-S(O)$_2$-NH-); R^7R^8N-S(O)$_2$-; C_{1-2}alkyl-C(O)-$R^{15a}N$-S(O)$_2$-; C_{1-4}alkyl-S(O)-, Ph-S(O)-, R^7R^8N-CO-; -NR^{15a}-C(O)R^{16a}; R^7R^8N; nitro (-NO_2); OH (including any tautomer thereof); C_{1-4}alkoxymethyl; C_{1-4}alkoxyethyl; C_{1-2}alkyl-S(O)$_2$-CH_2-; R^7R^8N-S(O)$_2$-CH_2-; C_{1-2}alkyl-S(O)$_2$-NR^{15a}-CH_2-; -CH_2-OH; -CH_2CH_2-OH; -CH_2-NR^7R^8; -CH_2-CH_2-NR^7R^8; -CH_2-C(O)OR^{30}; -CH_2-C(O)-NR^7R^8; -CH_2-NR^{15a}-C(O)-C_{1-3}alkyl; -$(CH_2)_n{}^{14}$-Het^1 where n^{14} is 0 or 1; cyano (-CN); Ar^{5b}; or phenyl, pyridinyl or pyrimidinyl wherein the phenyl, pyridinyl or pyrimidinyl independently are optionally substituted by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

and/or two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together and are: –CH=CH–CH=CH_2–, –$(CH_2)_n{}^{14a}$– where n^{14a} is 3, 4 or 5 (e.g. 3 or 4), –O–(CMe_2)–O–, –O–$(CH_2)_n{}^{14b}$–O– where n^{14b} is 1 or 2; -CH=CH-NR^{15b}-;

-N=CH-NR^{15b}-; -CH=N-NR^{15b}-; -N=N-NR^{15b}-; -CH=CH-O-; -N=CH-O-; -CH=CH-S-; or -N=CH-S-; wherein R^{15b} is H or C_{1-2}alkyl;

provided that:

two or more of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), nitrogen (N), or nitrogen-oxide (N^+-O^-);

and no more than two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-),

and no more than one of A, B, D, E and F is nitrogen-oxide (N^+-O^-);

and wherein, in sub-formula (z):

G is O or S or NR^9 wherein R^9 is a hydrogen atom (H), C_{1-4}alkyl, or C_{1-2}fluoroalkyl;

J is C-R^{6J}, C-[connection point to formula (I)], or nitrogen (N),
L is C-R^{6L}, C-[connection point to formula (I)], or nitrogen (N),
M is C-R^{6M}, C-[connection point to formula (I)], or nitrogen (N),
Q is C-R^{6Q}, C-[connection point to formula (I)], or nitrogen (N),

wherein, R^{6J}, R^{6L}, R^{6M} and R^{6Q} independently are: a hydrogen atom (H), a halogen atom; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-3}fluoroalkyl (e.g. C_{1-2}fluoroalkyl); C_{3-6}cycloalkyl; C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; OH (including any tautomer thereof); or phenyl optionally substituted by one or two substituents independently being fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

provided that:

two or more of J, L, M and Q are independently C-H, C-F, C-C_{1-2}alkyl (e.g. C-Me), C-[connection point to formula (I)], or nitrogen (N);

and no more than three of J, L, M and Q are nitrogen (N);

and wherein:

R^7 and R^8 are independently a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl such as methyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or R^7 and R^8 together are $-(CH_2)_n{}^{6}-$ or $-C(O)-(CH_2)_n{}^{7}-$ or $-C(O)-(CH_2)_n{}^{10}-C(O)-$ or $-(CH_2)_n{}^{8}-X^7-(CH_2)_n{}^{9}-$ or $-C(O)-X^7-(CH_2)_n{}^{10}-$ in which: n^6 is 3, 4, 5 or 6, n^7 is 2, 3, 4, or 5, n^8 and n^9 and n^{10} independently are 2 or 3, and X^7 is O or NR^{14};

R^{7a} is a hydrogen atom (H) or C_{1-4}alkyl;

R^{8a} is a hydrogen atom (H) or methyl;

R^{12} and R^{13} independently are H; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or R^{12} and R^{13} together are $-(CH_2)_n{}^{6a}-$ or $-C(O)-(CH_2)_n{}^{7a}-$ or $-C(O)-(CH_2)_n{}^{10a}-C(O)-$ or $-(CH_2)_n{}^{8a}-X^{12}-(CH_2)_n{}^{9a}-$ or $-C(O)-X^{12}-(CH_2)_n{}^{10a}-$ in which: n^{6a} is 3, 4, 5 or 6, n^{7a} is 2, 3, 4, or 5, n^{8a} and n^{9a} and n^{10a} independently are 2 or 3 and X^{12} is O or NR^{14a};

R^{14}, R^{14a}, R^{17} and R^{17a} independently are: a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-2}fluoroalkyl (e.g. CF_3); cyclopropyl; $-C(O)-C_{1-4}$alkyl (e.g. -C(O)Me); $-C(O)NR^{7a}R^{8a}$ (e.g. $-C(O)NH_2$); or $-S(O)_2-C_{1-4}$alkyl (e.g. $-S(O)_2Me$);

R^{15}, independent of other R^{15}, is a hydrogen atom (H); C_{1-4}alkyl (e.g. ^tBu or C_{1-2}alkyl e.g. methyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

R^{15a}, independent of other R^{15a}, is a hydrogen atom (H) or C_{1-4}alkyl;

R^{16} is: C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl); C_{3-6}cycloalkyl-CH_2- (e.g. C_{5-6}cycloalkyl-CH_2-); or phenyl or benzyl, wherein the phenyl and benzyl are independently optionally substituted on their ring by one or two substituents independently being fluoro, chloro, methyl, C_1fluoroalkyl, methoxy or C_1fluoroalkoxy;

R^{16a} is:
C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl);
C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl) optionally substituted by one oxo (=O), OH or C_{1-2}alkyl substituent (e.g. optionally substituted at the 3- or 4-position of a C_{5-6}cycloalkyl ring; and/or preferably unsubstituted C_{3-6}cycloalkyl);
C_{3-6}cycloalkyl-CH_2- (e.g. C_{5-6}cycloalkyl-CH_2-);

pyridinyl (e.g. pyridin-2-yl) optionally substituted on a ring carbon atom by one of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

Ar^{5c};

phenyl optionally substituted by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

benzyl optionally substituted on its ring by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or

a 4-, 5-, 6- or 7-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR^{27} where R^{27} is H, C_{1-2}alkyl or -C(O)Me; and wherein the ring is optionally substituted at carbon by one C_{1-2}alkyl or oxo (=O) substituent, provided that any oxo (=O) substituent is substituted at a ring-carbon atom bonded to a ring-nitrogen;

R^{30}, independent of other R^{30}, is a hydrogen atom (H), C_{1-4}alkyl or C_{3-6}cycloalkyl;

Ar^{5b} and Ar^{5c} independently is/are a 5-membered aromatic heterocyclic ring containing one O, S or NR^{15a} in the 5-membered ring, wherein the 5-membered ring can optionally additionally contain one or two N atoms, and wherein the heterocyclic ring is optionally substituted on a ring carbon atom by one of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, $-CH_2OH$, $-CH_2-OC_{1-2}$alkyl, OH (including the keto tautomer thereof) or $-CH_2-NR^{28}R^{29}$ wherein R^{28} and R^{29} independently are H or methyl; and

Het^1, is a 4-, 5-, 6- or 7-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR^{31} where R^{31} is H, C_{1-2}alkyl or -C(O)Me; and wherein the ring is optionally substituted at carbon by one C_{1-2}alkyl or oxo (=O) substituent, provided that any oxo (=O) substituent is substituted at a ring-carbon atom bonded to a ring-nitrogen;

provided that:

when R^3 is the heterocyclic group of sub-formula (bb), n^1 is 1, and Y is NR^{10}, then R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl; and

when R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^{10}, then R^{10} is not C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_{1-2}alkyl.

In compounds, for example in the compounds of formula (I) (or formula (IA) or formula (IB), see later), an "alkyl" group or moiety may be straight-chain or branched. Alkyl groups, for example C_{1-8}alkyl or C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl, which may be employed include C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, or n-hexyl or any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, isobutyl, 3-methylbutan-2-yl, 2-ethylbutan-1-yl, or the like.

A corresponding meaning is intended for "alkoxy", "alkylene", and like terms derived from alkyl. For example, "alkoxy" such as C_{1-6}alkoxy or C_{1-4}alkoxy or C_{1-2}alkoxy includes methoxy, ethoxy, propyloxy, and oxy derivatives of the alkyls listed above. "Alkylsulfonyl" such as C_{1-4}alkylsulfonyl includes methylsulfonyl (methanesulfonyl), ethylsulfonyl, and others derived from the alkyls listed above. "Alkylsulfonyloxy" such as C_{1-4}alkylsulfonyloxy includes methanesulfonyloxy (methylsulfonyloxy), ethanesulfonyloxy, *et al.*

"Cycloalkyl", for example C_{3-8}cycloalkyl, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Preferably, a C_{3-8}cycloalkyl group is C_{3-6}cycloalkyl or C_{5-6}cycloalkyl , that is contains a 3-6 membered or 5-6 membered carbocyclic ring.

"Fluoroalkyl" includes alkyl groups with one, two, three, four, five or more fluorine substituents, for example C_{1-4}fluoroalkyl or C_{1-3}fluoroalkyl or C_{1-2}fluoroalkyl such as monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl (CF_3CH_2-), 2,2-difluoroethyl (CHF_2CH_2-), 2-fluoroethyl (CH_2FCH_2-), etc. "Fluoroalkoxy" includes C_{1-4}fluoroalkoxy or C_{1-2}fluoroalkoxy such as trifluoromethoxy, pentafluoroethoxy, monofluoromethoxy, difluoromethoxy, etc. "Fluoroalkylsulfonyl" such as C_{1-4}fluoroalkylsulfonyl includes trifluoromethanesulfonyl, pentafluoroethylsulfonyl, etc.

A halogen atom ("halo") present in compounds, for example in the compounds of formula (I), means a fluorine, chlorine, bromine or iodine atom ("fluoro", "chloro", "bromo" or "iodo"), for example fluoro, chloro or bromo.

When the specification states that atom or moiety A is "bonded" or "attached" to atom or moiety B, it means that atom/moiety A is directly bonded to atom/moiety B usually by means of a covalent bond or a double covalent bond, and excludes A being indirectly attached to B via one or more intermediate atoms/moieties (e.g. excludes A-C-B); unless it is clear from the context that another meaning is intended.

When R^1 is C_{1-4}alkyl or C_{1-3}fluoroalkyl, it can be straight-chained or branched. Where R^1 is C_{1-4}alkyl then it can for example be methyl, ethyl, n-propyl, isopropyl or n-butyl. When R^1 is C_{1-3}fluoroalkyl, then R^1 can for example be C_1fluoroalkyl such as monofluoromethyl, difluoromethyl, trifluoromethyl; or R^1 can be C_2fluoroalkyl such as pentafluoroethyl or more preferably C_1fluoroalkyl-CH_2- such as 2,2,2-trifluoroethyl (CF_3CH_2-), 2,2-difluoroethyl (CHF_2CH_2-), or 2-fluoroethyl (CH_2FCH_2-).

Preferably, R^1 is C_{1-3}alkyl (e.g. methyl, ethyl or n-propyl), C_{1-3}fluoroalkyl or $-CH_2CH_2OH$. R^1 is more preferably C_{1-3}alkyl, C_{1-2}fluoroalkyl, or $-CH_2CH_2OH$. Still more preferably, R^1 is C_{2-3}alkyl (e.g. ethyl or n-propyl), C_2fluoroalkyl (e.g. C_1fluoroalkyl-CH_2- such as CF_3-CH_2-) or $-CH_2CH_2OH$; in particular ethyl, n-propyl or $-CH_2CH_2OH$. Yet more preferably, R^1 is C_2alkyl or C_2fluoroalkyl. R^1 is most preferably ethyl.

Preferably, R^2 is a hydrogen atom (H) or methyl, for example a hydrogen atom (H).

Preferably, in R^3 there is one substituent or no substituent.

In one optional embodiment, R^3 is the optionally substituted C_{3-8}cycloalkyl or the optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc).

In one optional embodiment, when R^3 is optionally substituted C_{3-8}cycloalkyl, it is not unsubstituted C_5cycloalkyl, i.e. not unsubstituted cyclopentyl. In this case, suitably, R^3 is optionally substituted C_{6-8}cycloalkyl.

When R^3 is optionally substituted C_{3-8}cycloalkyl, it is more suitablyoptionally substituted C_{6-7}cycloalkyl, preferably optionally substituted C_6cycloalkyl (i.e. optionally substituted cyclohexyl).

Suitably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being oxo (=O); OH; C_1alkoxy; C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy); NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-2}alkyl (more preferably R^{21} is H); C_{1-2}alkyl such as methyl; C_1fluoroalkyl such as $-CH_2F$ or $-CHF_2$; $-CH_2OH$; $-CH_2NHR^{22}$ wherein R^{22} is H; $-C(O)OR^{23}$ wherein R^{23} is H or methyl; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl; $-C(O)R^{25}$ wherein R^{25} is methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-4}alkyl); and wherein any OH, alkoxy, fluoroalkoxy or NHR^{21} substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc).

Preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently

being oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); C_{1-2}alkyl such as methyl; C_1fluoroalkyl such as $-CH_2F$ or $-CHF_2$; $-C(O)OR^{23}$ wherein R^{23} is H or methyl; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-2}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-2}alkyl).

More preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); methyl; $-CH_2F$; $-CHF_2$; $-C(O)OR^{23}$ wherein R^{23} is H; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl (preferably H); fluoro; hydroxyimino (=N-OH); or methoxyimino (=N-OR^{26} where R^{26} is methyl).

Still more preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being oxo (=O); OH; methyl; $-C(O)NHR^{24}$ wherein R^{24} is H; fluoro; hydroxyimino (=N-OH); or methoxyimino (=N-OR^{26} where R^{26} is methyl).

Yet more preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being OH; $-C(O)NHR^{24}$ wherein R^{24} is H; oxo (=O) or hydroxyimino (=N-OH).

In one optional embodiment, in R^3, the C_{3-8}cycloalkyl can be unsubstituted.

When R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, e.g. optionally substituted C_{5-8}cycloalkyl or C_{5-7}cycloalkyl, such as optionally substituted C_6cycloalkyl (optionally substituted cyclohexyl) or optionally substituted cyclohexenyl, the one or two optional substituents if present suitably can comprise a substituent (for example is or are substituent(s)) at the 3-, 4- and/or 5-position(s), e.g. at the 3- and/or 4- position(s), of the R^3 cycloalkyl or cycloalkenyl ring.

(In this connection and generally herein, the 1-position of the R^3 ring, e.g. of the R^3 cycloalkyl or cycloalkenyl ring is deemed to be the connection point to the -NH- in formula (I) = the ring atom connecting to the -NH- in formula (I)).

Suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, R^3 is not substituted (other than optionally by alkyl or fluoroalkyl) at the ring atom connecting to the -NH- in formula (I), and R^3 is not substituted (other than optionally by alkyl, fluoroalkyl or NHR^{21}) at the two ring atoms

either side of (bonded to) the connecting atom. For example, suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, R^3 is not substituted at the ring atom connecting to the -NH- in formula (I), and R^3 is not substituted at the two ring atoms either side of (bonded to) the connecting atom.

Suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, the one or two optional R^3 substituents if present can comprise a substituent (for example is or are substituent(s)):
(a) at the 3-position of a R^3 cyclobutyl ring, or
(b) at the 3- and/or 4- position(s) of a R^3 cyclopentyl or cyclopentenyl ring, or
(c) at the 3-, 4- and/or 5- position(s) of a R^3 cyclohexyl or cyclohexenyl ring, or
(d) at the 3-, 4-, 5- and/or 6- position(s) of a R^3 cycloheptyl or cycloheptenyl ring, or
(e) at the 3-, 4-, 5-, 6- and/or 7- position(s) of a R^3 cyclooctyl ring,
and/or
(f) at the 1-, 2- and/or highest-numbered- position(s) of a R^3 cycloalkyl or cycloalkenyl ring, for alkyl or fluoroalkyl substituent(s), and/or
(g) at the 2- and/or highest-numbered- position(s) of a R^3 cycloalkyl or cycloalkenyl ring, for NHR^{21} or fluoro substituent(s).

When R^3 is optionally substituted C_{3-8}cycloalkyl, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) is suitably at the 3-, 4- or 5- position, e.g. 3- or 5-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl) ring. Optionally, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) can be: at the 3-position of a R^3 cyclobutyl ring; or at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) ring; or at the 3-, 4- or 5- position of a R^3 C_6cycloalkyl (cyclohexyl) ring (e.g. at the 3- or 5-position of a R^3 cyclohexyl ring especially for any OH substituent); or at the 3-, 4-, 5- or 6- position of a R^3 cycloheptyl ring, or at the 3-, 4-, 5-, 6- or 7- position of a R^3 cyclooctyl ring. Suitably, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) is at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) ring; or more suitably at the 3-, 4- or 5- position, still more suitably at the 3- or 5-position, of a R^3 C_6cycloalkyl (cyclohexyl) ring.

Suitably, when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, any $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$, $-CH_2OH$ or fluoro substituent is: at the 3-position of a R^3 cyclobutyl ring; or at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) or cyclopentenyl ring; or at the 3-, 4- or 5- position,

preferably at the 4-position, of a R^3 C_6cycloalkyl (cyclohexyl) or cyclohexenyl ring; or at the 3-, 4-, 5- or 6- position of a R^3 cycloheptyl or cycloheptenyl ring, or at the 3-, 4-, 5-, 6- or 7- position of a R^3 cyclooctyl ring. Any $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$, $-CH_2OH$ or fluoro substituent, e.g. any $-C(O)NHR^{24}$ or fluoro substituent, is suitably at the 3-, 4- or 5- position, more suitably at the 4-position, of a R^3 C_6cycloalkyl (cyclohexyl) or cyclohexenyl ring. It is particularly preferable for any $-C(O)NHR^{24}$ substituent to be at the 4-position of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl, any NHR^{21} substituent is at any position other than the 1-position (the ring atom connecting to the -NH- in formula (I)), e.g. at the 2-, 3-, 4-, 5-, 6-, 7- or 8- position. Suitably, any NHR^{21} substituent is at the 2-, 3-, 5- or 6- position, or more suitably at the 3- or 5- position, of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, any alkyl or fluoroalkyl substituent can for example be at the 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8- position, for example at the 1-, 2-, 3-, 5- or 6- position, e.g. the 1-position, of the R^3 ring. Preferably, any alkyl or fluoroalkyl substituent is at the 1-, 2-, 3-, 5- or 6- position, or more preferably at the 1-, 3- or 5- position, of a R^3 cyclohexyl or cyclohexenyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl, any oxo (=O), hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino ($=N-OR^{26}$) substituent is suitably at the 3-, 4- or 5- position, e.g. at the 4-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl e.g. cyclohexyl) ring. Preferably any such substituent is at the 4-position of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl), R^3 is preferably cyclohexyl (i.e. unsubstituted); or cycloheptyl (i.e. unsubstituted); or cyclohexyl substituted by one substituent being oxo (=O), OH, NHR^{21}, C_{1-2}alkyl, C_{1-2}fluoroalkyl, $-CH_2OH$, $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$, fluoro, hydroxyimino (=N-OH), or (C_{1-4}alkoxy)imino ($=N-OR^{26}$); or cyclohexyl substituted by two fluoro substituents. More preferably, R^3 is cyclohexyl (i.e. unsubstituted); or cycloheptyl (i.e. unsubstituted); or cyclohexyl substituted by one substituent being oxo (=O), OH, NHR^{21}, C_{1-2}alkyl, C_{1-2}fluoroalkyl, $-C(O)OR^{23}$, $-C(O)NHR^{24}$, fluoro, hydroxyimino (=N-OH), or (C_{1-2}alkoxy)imino ($=N-OR^{26}$ wherein R^{26} is C_{1-2}alkyl); or cyclohexyl substituted by two fluoro substituents. Still more preferably R^3 is cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O), hydroxyimino (=N-OH), $-C(O)NH_2$, methyl or OH substituent. The optional substituent can for example be at the 3- or 4- position, of the R^3 cyclohexyl ring. Preferably, any OH substituent is preferably at the 3-position of

a R^3 cyclohexyl ring, and/or any oxo (=O), hydroxyimino (=N-OH), (C_{1-4}alkoxy)imino (=N-OR^{26}) or -C(O)NH_2 substituent is preferably at the 4-position of a R^3 cyclohexyl ring, and/or any alkyl or fluoroalkyl substituent is preferably at the 1-, 3- or 5- position of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{6-7}cycloalkyl, R^3 can for example be 4-hydroxy-cyclohexyl (i.e. 4-hydroxycyclohexan-1-yl), 4-methylcyclohexyl, 3-fluorocyclohexyl, 2-aminocyclohexyl, 3-(HO(O)C)cyclohexyl or 3-oxocyclohexyl, but R^3 is more preferably cyclohexyl (i.e. unsubstituted), cycloheptyl (i.e. unsubstituted), 3-hydroxy-cyclohexyl (i.e. 3-hydroxycyclohexan-1-yl) (e.g. in a *cis* configuration), 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl), 4-(hydroxyimino)cyclohexyl (i.e. 4-(hydroxyimino)cyclohexan-1-yl), 4-(C_{1-2}alkoxyimino)cyclohexyl, 4-(aminocarbonyl)cyclohexyl (i.e. 4-(aminocarbonyl)cyclohexan-1-yl) (e.g. in a *cis* configuration), 1-methylcyclohexyl, 3-methylcyclohexyl, 4,4-(difluoro)cyclohexyl, or 3-aminocyclohexyl.

When R^3 is optionally substituted C_{6-7}cycloalkyl, R^3 is most preferably cyclohexyl (i.e. unsubstituted), 3-hydroxy-cyclohexyl (i.e. 3-hydroxycyclohexan-1-yl) (e.g. in a *cis* configuration), 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl), 4-(hydroxyimino)cyclohexyl (i.e. 4-(hydroxyimino)cyclohexan-1-yl), or 4-(aminocarbonyl)cyclohexyl (i.e. 4-(aminocarbonyl)cyclohexan-1-yl) (e.g. in a *cis* configuration).

When R^3 is optionally substituted C_5cycloalkyl (optionally substituted cyclopentyl), R^3 can for example be cyclopentyl (i.e. unsubstituted) or more suitably 3-hydroxy-cyclopentyl.

When R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, preferably it is optionally substituted mono-unsaturated-C_{5-6}cycloalkenyl, more preferably optionally substituted mono-unsaturated-C_6cycloalkenyl (i.e. optionally substituted mono-unsaturated-cyclohexenyl = optionally substituted cyclohexenyl). For example, the R^3 cyclohexenyl can be optionally substituted cyclohex-3-en-1-yl.

When R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, in one optional embodiment the R^3 cycloalkenyl is optionally substituted with one or two substituents independently being fluoro or methyl. Preferably, in this embodiment, if there are two substituents then they are not both methyl.

In another optional embodiment, the R^3 cycloalkenyl (e.g. cyclohexenyl) is optionally substituted with one substituent being fluoro or C_{1-2}alkyl (preferably fluoro or methyl); more preferably the R^3 cycloalkenyl (e.g. cyclohexenyl) is substituted with one fluoro

substituent or is unsubstituted. For example, the R^3 optionally substituted cycloalkenyl can be cyclohex-3-en-1-yl (i.e. unsubstituted) or 4-fluoro-cyclohex-3-en-1-yl.

For R^3 cycloalkenyl, the optional substituent(s) can for example be at the 1-, 2-, 3-, 4-, 5- or 6- position(s) of the cycloalkenyl ring.

When R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then Y is preferably O or NR^{10}, most preferably O or N-C(O)-NH_2.

Suitably, R^{10} is a hydrogen atom (H), methyl, ethyl, C(O)NH_2, C(O)-C_{1-2}alkyl or C(O)-C_1fluoroalkyl. Preferably, R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl. Suitably, R^{10} is not $CH_2C(O)NH_2$.

More preferably, R^{10} is a hydrogen atom (H), C(O)NH_2, C(O)-C_{1-2}alkyl (e.g. C(O)methyl) or C(O)-C_1fluoroalkyl (e.g. C(O)-CF_3). Still more preferably R^{10} is H, C(O)NH_2 or C(O)methyl; for example C(O)NH_2.

When R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then it is preferable that R^3 is the heterocyclic group of sub-formula (aa) or (bb), more preferably of sub-formula (bb).

In sub-formula (bb), n^1 is preferably 1. In sub-formula (cc), n^2 is preferably 1. That is, six-membered rings are preferred in the R^3 heterocyclic group.

Suitably, in R^3, the heterocyclic group of sub-formula (aa), (bb) or (cc) is unsubstituted on a ring carbon. (In this connection, where Y is NR^{10}, R^{10} is not a substituent on a ring carbon).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents preferably comprise (e.g. is or independently are) OH; oxo (=O); C_{1-2}alkyl (e.g. methyl) or C_{1-2}fluoroalkyl (e.g. C_1fluoroalkyl such as -CH_2F or -CHF_2). More preferably, in the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents comprise (e.g. is or independently are) C_{1-2}alkyl (e.g. methyl) or oxo; most preferably the one or two optional substituents comprise (e.g. is or are) oxo (=O).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any oxo (=O) substituent is preferably on a carbon atom bonded (adjacent) to Y, e.g. is on a carbon atom bonded (adjacent) to Y only when Y is O or NR^{10}.

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any oxo (=O) substituent can suitably be at the 2-, 3-, 4-, 5- or 6- position of the R^3 heterocyclic ring. For example any oxo (=O) substituent(s) can be: at the 2-, 4- or 5- position(s) (e.g. 2-position or 4-position, or two oxo substituents at 2- and 4- positions) of a R^3 heterocyclic group of sub-formula (aa), at the 2-, 4-, 5- or 6- position(s) (e.g. 4-position) of a six-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 1, at the 2-, 3-, 5-, 6- or 7-position(s) (e.g. 5-position) of a seven-membered R^3 heterocyclic group of sub-formula (bb) wherein n^1 is 2, or at the 2-, 4-, 5-, 6- or 7- position(s) (e.g. 2-position) of a seven-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 2.

(In this connection and generally herein, the 1-position of the R^3 heterocyclic ring is deemed to be the connection point to the -NH- in formula (I) = the ring atom connecting to the -NH- in formula (I), and the remaining positions of the ring are then numbered so that the ring heteroatom takes the lowest possible number).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any alkyl or fluoroalkyl substituent can for example be at the 1-, 2-, 3-, 4-, 5- or 6- position, e.g. the 1-position, of the R^3 heterocyclic ring, for example at the 1-, 3- or 5- position of a six-membered R^3 heterocyclic ring.

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any OH substituent can be: at the 5-position of a six-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 1; at the 5- or 6- position of a seven-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 2; or at the 6- position of a seven-membered R^3 heterocyclic group of sub-formula (bb) wherein n^1 is 2.

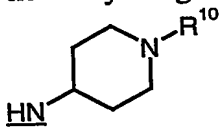
Any other substituents of the R^3 heterocyclic group can optionally be positioned on the R^3 heterocyclic ring at numerical positions as described herein for when R^3 is optionally substituted C_{5-7}cycloalkyl, all necessary changes to the wording being made.

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), preferably, only C_{1-2}alkyl, C_{1-2}fluoroalkyl, fluoro or oxo (=O) substitution or no substitution is allowed independently at each of the 2- and highest-numbered- positions of the R^3 heterocyclic ring (e.g. at each of the 2- and 6- positions of a six-membered R^3 heterocyclic ring), and/or only C_{1-2}alkyl, C_{1-2}fluoroalkyl or fluoro substitution or no substitution is allowed at the 1-position of the R^3 heterocyclic ring.

When R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^{10}, then R^{10} is not C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_{1-2}alkyl. According to one optional embodiment, when R^3 is the heterocyclic group of sub-formula (aa) and Y is

NR^{10} then R^{10} is optionally not C(O)NHMe, C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_{1-2}alkyl.

In one preferable embodiment, Y is O, S, SO_2 or NH when R^3 is the heterocyclic group of sub-formula (aa).

When R^3 is the heterocyclic group of sub-formula (bb), n^1 is 1, and Y is NR^{10} (e.g. when NHR^3 is ), then R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl. More preferably, when R^3 is the heterocyclic group of sub-formula (bb) wherein n^1 is 1 or 2 and Y is NR^{10}, then R^{10} is preferably not C_{1-2}alkyl or C_{1-2}fluoroalkyl.

In one embodiment, when R^3 is the heterocyclic group of sub-formula (bb), then preferably Y is O, S, SO_2 or NR^{10} wherein R^{10} is H, $C(O)NH_2$, C(O)-C_{1-2}alkyl (e.g. C(O)methyl) or C(O)-C_1fluoroalkyl (e.g. C(O)-CF_3), or more preferably R^{10} is H, $C(O)NH_2$ or C(O)Me, for example $C(O)NH_2$ or C(O)Me, most preferably $C(O)NH_2$.

In one optional embodiment, when R^3 is the heterocyclic group of sub-formula (cc), then optionally Y is O, S, SO_2 or NR^{10} wherein R^{10} is H, $C(O)NH_2$, C(O)-C_{1-2}alkyl (e.g. C(O)methyl) or C(O)-C_1fluoroalkyl (e.g. C(O)-CF_3). In this case R^{10} can for example be H, $C(O)NH_2$ or C(O)Me, for example H.

Optionally, for sub-formula (bb) and/or for sub-formula (cc), Y is O or NR^{10}.

When R^3 is optionally substituted C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc), then a substituent can be in the *cis* or *trans* configuration with respect to the -NH- group of formula (I) to which R^3 is attached (bonded); this includes mixtures of configurations wherein the stated configuration is the major component. For example, an OH or $-C(O)NHR^{24}$ substituent on C_{6-7}cycloalkyl can for example be in the *cis* configuration and/or a NHR^{21} substituent on C_{6-7}cycloalkyl can for example be in the *cis* or *trans* configuration, with respect to the -NH- group of formula (I) to which R^3 is attached (bonded), including mixtures of configurations wherein the stated configuration is the major component.

When R^3 is a bicyclic group of sub-formula (ee), then preferably Y^1, Y^2 and Y^3 are all CH_2.

Preferably, NHR^3 is of sub-formula (a), (a1), (b), (c), (c 1), (c 2), (c 3), (c 4), (c 5), (c 6), (c 7), (d), (e), (f), (g), (g1), (g2), (g3), (g4), (h), (i), (j), (k), (k1), (k2), (L), (m), (m1), (m2), (m3), (m5), (n), (o), (o1), (o2), (o3), (p), (p1), (p2), (p3), (p4), (p5), (p6), (p7), (p8), (p9), (p10), (p11) or (q):

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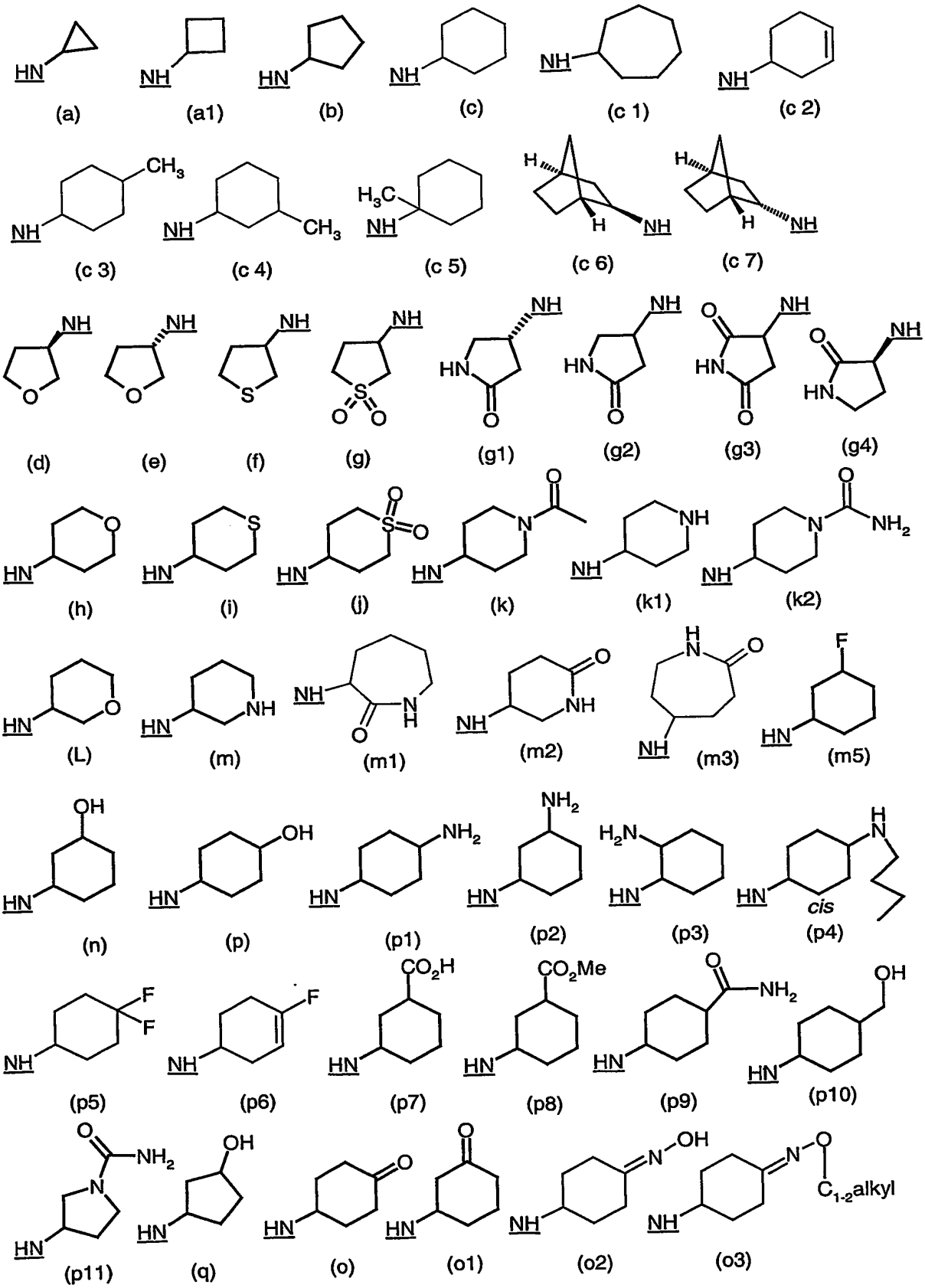
(a)
(a1)
(b)
(c)
(c 1)
(c 2)
(c 3)
(c 4)
(c 5)
(c 6)
(c 7)
(d)
(e)
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(p8)
(p9)
(p10)
(p11)
(q)
(o)
(o1)
(o2)
(o3)
C1-2alkyl

In the sub-formulae (a) to (q) etc above, the -NH- connection point of the NHR^3 group to the 4-position of the pyrazolopyridine of formula (I) is underlined.

Preferably, NHR^3 is of sub-formula (c), (c1), (c 2), (c 3), (c 4), (c 5), (c 6), (c 7), (d), (e), (f), (g1), (g4), (h), (i), (j), (k), (k1), (k2), (L), (m), (m1), (m2), (m3), (m5), (n), (o), (o1), (o2), (o3), (p), (p2), (p5), (p6), (p7), (p9), (p10), (p11) or (q). More preferably, NHR^3 is of sub-formula (c), (c1), (c 4), (c 5), (h), (i), (j), (k), (k2), (m1), (m2), (n), (o), (o2), (o3), (p2), (p5), (p6), (p9), (p11) or (q). NHR^3 can for example be of sub-formula (c), (p11), (h), (k), (k2), (n), (o), (o2) or (p9); or still more preferably (c), (p11), (h), (k2), (n), (o), (o2) or (p9). Most preferably, R^3 is tetrahydro-2H-pyran-4-yl or 1-(aminocarbonyl)-4-piperidinyl; that is NHR^3 is most preferably of sub-formula (h) or (k2), as shown above.

When NHR^3 is of sub-formula (n), then preferably it is in the *cis* configuration, i.e. preferably it is a *cis*-(3-hydroxycyclohexan-1-yl)amino group, e.g. in any enantiomeric form or mixture of forms such as a racemic mixture.

When NHR^3 is of sub-formula (p9), then preferably it is in the *cis* configuration, i.e. preferably it is a *cis*-[4-(aminocarbonyl)cyclohexan-1-yl]amino group.

Where R^4 is C_{1-2}fluoroalkyl, then it can be C_1fluoroalkyl such as monofluoromethyl, difluoromethyl or trifluoromethyl.

R^{4a} can suitably be a hydrogen atom (H) or methyl (Me), more suitably H.

R^4 can for example be a hydrogen atom (H); methyl, ethyl, C_1fluoroalkyl, $-CH_2OH$, $-CH(Me)OH$, $-CH_2CH_2OH$, or $-CH_2OMe$; or preferably a hydrogen atom (H), methyl, ethyl, CF_3, $-CH_2OH$, or $-CH_2OMe$. More preferably, R^4 is methyl, ethyl, CF_3, $-CH_2OH$, or $-CH_2OMe$; for example methyl, ethyl, CF_3 or $-CH_2OH$. Still more preferably, R^4 is methyl or ethyl. Most preferably, R^4 is ethyl.

Suitably, R^4 is not a hydrogen atom (H), and more suitably R^5 is a hydrogen atom (H).

When R^5 is C_{1-4}alkyl substituted by one substituent R^{11} or R^5 is C_{2-4}alkyl (e.g. ethyl or n-propyl) substituted on different carbon atoms by two OH substituents, then suitably R^5 is C_{1-4}alkyl substituted by one substituent R^{11}.

When R^5 is C_{1-4}alkyl substituted by one substituent R^{11}, it is suitable that R^5 is C_{1-3}alkyl (e.g. C_{1-2}alkyl) substituted by one substituent R^{11}. Suitably, R^5 is $-(CH_2)_{n^5}$-R^{11} wherein n^5 is 1, 2, 3 or 4 or R^5 is -CH(Me)-R^{11}. Preferably n^5 is 1, 2 or 3, more preferably 1 or 2, still more preferably 1.

Suitably, R^{11} is: hydroxy (OH); C_{1-4}alkoxy or C_{1-2}alkoxy (such as t-butyloxy, ethoxy or preferably methoxy); C_1fluoroalkoxy; $-NR^{12}R^{13}$; $-NR^{15}$-C(O)R^{16}; or $-NR^{15}$-$S(O)_2R^{16}$. More suitably, R^{11} is hydroxy (OH), C_{1-4}alkoxy (e.g. C_{1-2}alkoxy), or $-NR^{12}R^{13}$; still more suitably OH, ethoxy, methoxy, NH_2, NHMe, NHEt, NMe_2, pyrrolidin-1-yl or piperidin-1-yl; preferably OH, methoxy, NH_2, NHMe or NMe_2.

Where R^5 is C_{1-8}alkyl, then suitably it is C_{1-6}alkyl or C_{1-5}alkyl or C_{1-4}alkyl or C_{1-3}alkyl. Where R^5 is C_{1-3}fluoroalkyl then suitably it is C_{1-2}fluoroalkyl or C_1fluoroalkyl such as monofluoromethyl, difluoromethyl or trifluoromethyl. Where R^5 is C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group, then optionally the C_{3-8}cycloalkyl is not substituted at the connecting ring-carbon. Where R^5 is optionally substituted C_{3-8}cycloalkyl, then suitably it is C_{3-8}cycloalkyl (i.e. unsubstituted) and/or optionally substituted C_{3-6}cycloalkyl such as optionally substituted cyclopropyl or optionally substituted cyclohexyl.

When R^5 is optionally substituted $-(CH_2)_{n^4}$-C_{3-8}cycloalkyl, then n^4 is preferably 1, and/or suitably R^5 is optionally substituted $-(CH_2)_{n^4}$-C_{3-6}cycloalkyl such as optionally substituted $-(CH_2)_{n^4}$-cyclopropyl or optionally substituted $-(CH_2)_{n^4}$-C_6cycloalkyl. When R^5 is optionally substituted $-(CH_2)_{n^4}$-C_{3-8}cycloalkyl, preferably it is not substituted. For example, R^5 can be (cyclohexyl)methyl-, that is $-CH_2$-cyclohexyl, or $-CH_2$-cyclopropyl.

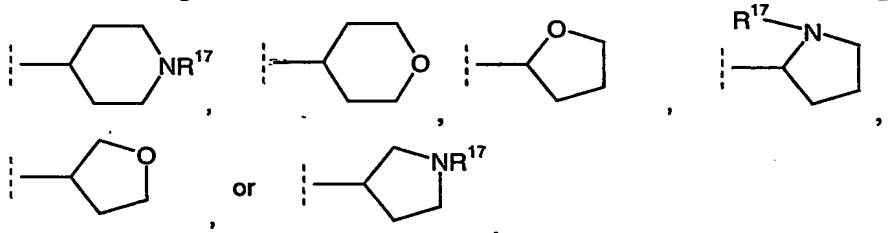
When R^{19} is C_{1-2}alkyl, then optionally it can be methyl.

When R^5 is $-(CH_2)_{n^{11}}$-C(O)R^{16}; $-(CH_2)_{n^{11}}$-C(O)$NR^{12}R^{13}$; $-CHR^{19}$-C(O)$NR^{12}R^{13}$; $-(CH_2)_{n^{11}}$-C(O)OR^{16}; $-(CH_2)_{n^{11}}$-C(O)OH; $-CHR^{19}$-C(O)OR^{16}; $-CHR^{19}$-C(O)OH; $-(CH_2)_{n^{11}}$-$S(O)_2$-$NR^{12}R^{13}$; $-(CH_2)_{n^{11}}$-$S(O)_2R^{16}$; or $-(CH_2)_{n^{11}}$-CN; then R^5 can suitably be $-(CH_2)_{n^{11}}$-C(O)$NR^{12}R^{13}$; $-(CH_2)_{n^{11}}$-C(O)OR^{16}; $-(CH_2)_{n^{11}}$-C(O)OH; or $-(CH_2)_{n^{11}}$-CN; more suitably $-(CH_2)_{n^{11}}$-C(O)OR^{16} or $-(CH_2)_{n^{11}}$-CN; or preferably $-(CH_2)_{n^{11}}$-C(O)OR^{16}.

Preferably, n^{11} is 0, 1 or 2; more preferably n^{11} is 0 or 1, for example 0.

When R^5 is $-(CH_2)_n{}^{13}$-Het, n^{13} can for example be 0 or 1.

Suitably, Het is a 5- or 6-membered saturated or unsaturated heterocyclic ring, and/or preferably Het is a 4-, 5-, 6- or 7-membered saturated heterocyclic ring.Suitably, the heterocyclic ring Het contains one ring-hetero-atom selected from O, S and N. Suitably, the carbon ring-atoms in Het are not substituted. Het can for example be:



When R^5 is phenyl (Ph), $-CH_2$-Ph, -CHMe-Ph, -CHEt-Ph, CMe_2Ph, or $-CH_2CH_2$-Ph, wherein the phenyl ring Ph is optionally substituted, then suitably Ph is optionally substituted with one of the substituents defined herein. Preferably, R^5 is phenyl (Ph) or $-CH_2$-Ph wherein the phenyl ring Ph is optionally substituted with one or two substituents as defined herein.

When R^5 is phenyl (Ph), $-CH_2$-Ph, -CHMe-Ph, -CHEt-Ph, CMe_2Ph, or $-CH_2CH_2$-Ph, wherein the phenyl ring Ph is optionally substituted with one or two substituents, then preferably the phenyl ring Ph is optionally substituted with one or two (e.g. one) substituents independently being: fluoro; chloro; C_{1-2}alkyl (e.g. methyl); C_1fluoroalkyl (e.g. trifluoromethyl); C_{1-2}alkoxy (e.g. methoxy); or C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy). Ph can be unsubstituted.

When R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-(CH_2)_p{}^3$-X^5-$(CH_2)_p{}^4$-, in which X^5 is O or NR^{17a}; then preferably R^4 and R^5 taken together are $-(CH_2)_p{}^1-$. In one embodiment of the invention, R^4 and R^5 are not taken together to be either $-(CH_2)_p{}^1-$ or $-(CH_2)_p{}^3$-X^5-$(CH_2)_p{}^4$-.

When R^4 and R^5 taken together are $-(CH_2)_p{}^1-$, then p^1 can for example be 2, 4, 5 or 6. p^1 is preferably 2, 4 or 5, more preferably 2 or 4.

When R^4 and R^5 taken together are $-(CH_2)_p{}^3$-X^5-$(CH_2)_p{}^4$-, in which X^5 is O or NR^{17a}; then suitably: p^3 is 2, and/or p^4 is 2, and/or one of p^3 and p^4 is 1 and the other of p^3 and p^4 is 2, and/or p^3 and p^4 are both 1. Suitably, X^5 is O. $-(CH_2)_p{}^3$-X^5-$(CH_2)_p{}^4$- can for example be $-(CH_2)_2$-O-$(CH_2)_2$-.

In one embodiment of the invention, R^4 and R^5 are not taken together as $-(CH_2)_p{}^1-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$.

It is preferable that Ar has the sub-formula (x).

Preferably, in sub-formula (x), two or more (more preferably three or more) of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine) or nitrogen (N).

Preferably, in sub-formula (x), three or more of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), nitrogen (N), or nitrogen-oxide (N^+-O^-).

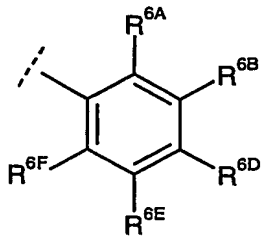
Preferably, in sub-formula (x), two or more (e.g. three or more) of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), or nitrogen (N); and one or more (e.g. two or more) others of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), C-Cl (carbon-chlorine), C-Me, C-OMe, or nitrogen (N). More preferably, in sub-formula (x), two or more (e.g. three or more) of A, B, D, E and F are C-H (carbon-hydrogen); and one or more (e.g. two or more) others of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), C-Cl (carbon-chlorine), C-Me, C-OMe, or nitrogen (N).

Preferably, in sub-formula (x), two or more (e.g. three or more, e.g. four or more) of A, B, D, E and F are C-H.

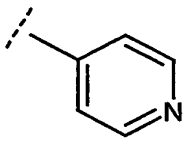
Preferably, in sub-formula (x), no more than one (more preferably none) of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-).

Preferably, in sub-formula (x), none of A, B, D, E and F are nitrogen-oxide (N^+-O^-).

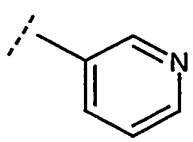
Preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x2), (x3), (x4), (x5), (x6), (x7), (x8), (x9), (x10), (x11), (x12), (x13), (x14), (x15) or (x16):



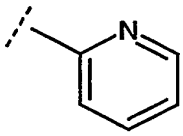
(x1)



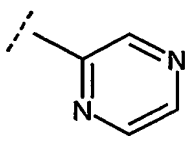
(x2)



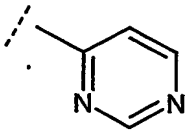
(x3)



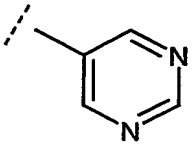
(x4)



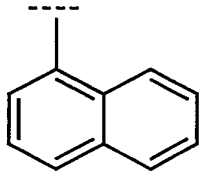
(x5)



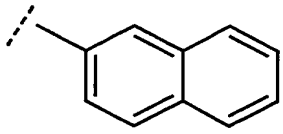
(x6)



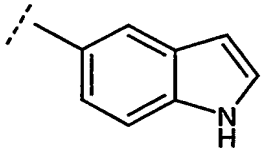
(x7)



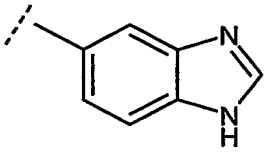
(x8)



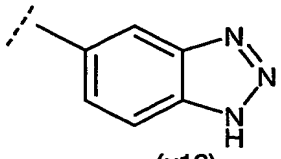
(x9)



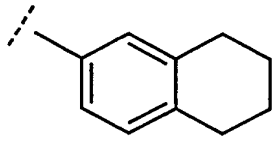
(x10)



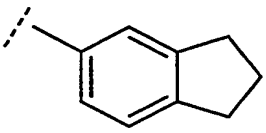
(x11)



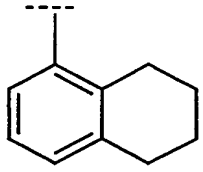
(x12)



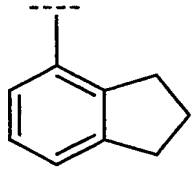
(x13)



(x14)



(x15)



(x16)

More preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x2), (x3), (x8), (x13), or (x14). Still more preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x8), (x13), or (x14). Most preferably, Ar has the sub-formula (x) which is sub-formula (x1).

In sub-formula (x), preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine, bromine or iodine atom, methyl, ethyl, n-propyl, isopropyl, C_4alkyl, trifluoromethyl, -CH_2OH, methoxy, ethoxy, n-propoxy, isopropoxy, C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy), cyclohexyloxy; cyclopentyloxy; nitro (-NO_2), OH, C_{1-3}alkylS(O)$_2$- (such as MeS(O)$_2$-), C_{1-3}alkylS(O)$_2$-NH- such as Me-S(O)$_2$-NH-, Me_2N-S(O)$_2$-, H_2N-S(O)$_2$-, -$CONH_2$, -CONHMe, -C(O)OH, cyano (-CN), NMe_2, or C_{1-2}alkyl-S(O)$_2$-CH_2- such as Me-S(O)$_2$-CH_2-.

More preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine, bromine or iodine atom, methyl, ethyl, n-propyl, isopropyl, isobutyl, trifluoromethyl, -CH_2OH, methoxy, ethoxy, n-propoxy, isopropoxy, C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy), nitro (-NO_2), OH, C_{1-3}alkylS(O)$_2$- such as MeS(O)$_2$-, C_{1-2}alkylS(O)$_2$-NH- such as Me-S(O)$_2$-NH-, -$CONH_2$, cyano (-CN), or C_{1-2}alkylS(O)$_2$-CH_2- such as Me-S(O)$_2$-CH_2.

Still more preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine or bromine atom, methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, -CH_2OH, methoxy, ethoxy, n-propoxy, difluoromethoxy, OH or MeS(O)$_2$-.

When two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together, then, preferably, when taken together they are: –CH=CH–CH=CH_2–, –$(CH_2)_n{}^{14a}$– where n^{14a} is 3, 4 or 5 (e.g. 3 or 4), –O–(CMe_2)–O–, –O–$(CH_2)_n{}^{14b}$–O– where n^{14b} is 1 or 2; -CH=CH-NR^{15b}-; -N=CH-NR^{15b}-; -N=N-NR^{15b} wherein R^{15b} is H or C_{1-2}alkyl (preferably R^{15b} is H). More preferably, in this embodiment, two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together and are: –CH=CH–CH=CH_2– or –$(CH_2)_n{}^{14a}$– where n^{14a} is 3, 4 or 5 (e.g. 3 or 4).

In sub-formula (x), e.g. in sub-formula (x1), suitably, one, two or three of R^{6B}, R^{6D} and R^{6E} are other than a hydrogen atom (H).

In sub-formula (x), e.g. in sub-formula (x1), preferably, one or both of R^{6A} and R^{6F} are independently a hydrogen atom (H), a fluorine atom (F), or methyl. For example, one or both of R^{6A} and R^{6F} can be a hydrogen atom (H).

In sub-formula (x), e.g. in sub-formula (x1), suitably the ring or ring system is unsubstituted, monosubstituted, disubstituted or trisubstituted; or preferably the ring or ring system is unsubstituted, monosubstituted or disubstituted; more preferably monosubstituted or disubstituted. In sub-formula (x), e.g. in sub-formula (x1), for monosubstitution of the ring or ring system, then the one substituent selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} is suitably present at the 3- or 4-position with respect to the –(CR^4R^5)– side-chain (i.e. D is CR^{6D} where R^{6D} is other than H), or is a 2-methyl, 2-ethyl, 2-fluoro or 2-chloro substituent. In sub-formula (x), e.g. in sub-formula (x1), for disubstitution of the ring or ring system, then 3,4-disubstitution, 2,4-disubstitution, 2,3-disubstitution or 3,5-disubstitution is suitable.

In one preferable embodiment, Ar has the sub-formula (x1) and is: phenyl, monoalkyl-phenyl-, mono(fluoroalkyl)-phenyl-, monohalo-phenyl-, monoalkoxy-phenyl-, mono(fluoroalkoxy)-phenyl-, mono(N,N-dimethylamino)-phenyl-,

mono(methyl-SO_2-NH-)-phenyl-, mono(methyl-SO_2-)-phenyl-, dialkyl-phenyl-, monoalkyl-monohalo-phenyl-, mono(fluoroalkyl)-monohalo-phenyl-, dihalo-phenyl-, dihalo-monoalkyl-phenyl-, dihalo-mono(hydroxymethyl)-phenyl- (e.g. 2,3-dichloro-6-(hydroxymethyl)-phenyl-), or dialkoxy-phenyl- such as 3,4-dimethoxy-phenyl-. The substituents can preferably be further defined, as defined in preferable embodiments herein.

In one preferable embodiment, Ar is of sub-formula (x1) and is: monoalkyl-phenyl-, mono(fluoroalkyl)-phenyl-, monohalo-phenyl-, monoalkoxy-phenyl-, mono(fluoroalkoxy)-phenyl-, dialkyl-phenyl-, monoalkyl-monohalo-phenyl-, dihalo-phenyl- or dihalo-monoalkyl-phenyl-.

More preferably, in this embodiment, Ar is:
- monoC_{1-4}alkyl-phenyl- or monoC_{1-3}alkyl-phenyl- such as 4-C_{1-4}alkyl-phenyl- (e.g. 4-C_{1-3}alkyl-phenyl-) or 2-C_{1-2}alkyl-phenyl-;
- monoC_1fluoroalkyl-phenyl- such as 4-C_1fluoroalkyl-phenyl-;
- monoC_{1-3}alkoxy-phenyl- such as 4-C_{1-3}alkoxy-phenyl- or 3-C_{1-3}alkoxy-phenyl-;
- mono(C_1fluoroalkoxy)-phenyl- such as 4-C_1fluoroalkoxy-phenyl-;
- diC_{1-3}alkyl-phenyl- or diC_{1-2}alkyl-phenyl- or dimethyl-phenyl- such as 3,4-dimethyl-phenyl-, 2,4-dimethyl-phenyl-, 3,5-dimethyl-phenyl-, 2,3-dimethyl-phenyl- or 2,5-dimethyl-phenyl-; for example 3,4-dimethyl-phenyl-, 2,4-dimethyl-phenyl-, 2,3-dimethyl-phenyl- or 3,5-dimethyl-phenyl-;
- monoC_{1-3}alkyl-monohalo-phenyl-, such as monoC_{1-2}alkyl-monohalo-phenyl- and/or monoC_{1-3}alkyl-monochloro-phenyl- or monoC_{1-3}alkyl-monofluoro-phenyl-, for example 4-methyl-3-chloro-phenyl-, 3-methyl-4-chloro-phenyl-, or 2-methyl-4-chloro-phenyl-;
- dihalo-phenyl- such as 2-chloro-4-fluorophenyl- or 2,4-difluoro-phenyl- or 4-bromo-2-fluorophenyl- or preferably 4-chloro-2-fluorophenyl-; for example dichloro-phenyl- such as 3,4-dichloro-phenyl- or 2,4-dichloro-phenyl- or 2,6-dichloro-phenyl- or preferably 2,3-dichloro-phenyl-; or
- dihalo-monoC_{1-2}alkyl-phenyl- e.g. 2,4-dichloro-6-methyl-phenyl-.

In an alternative embodiment, Ar has the sub-formula (z).

Preferably, in sub-formula (z), three or more (for example all) of J, L, M and Q are independently C-H, C-F, C-C_{1-2}alkyl (e.g. C-Me), C-[connection point to formula (I)], or nitrogen (N).

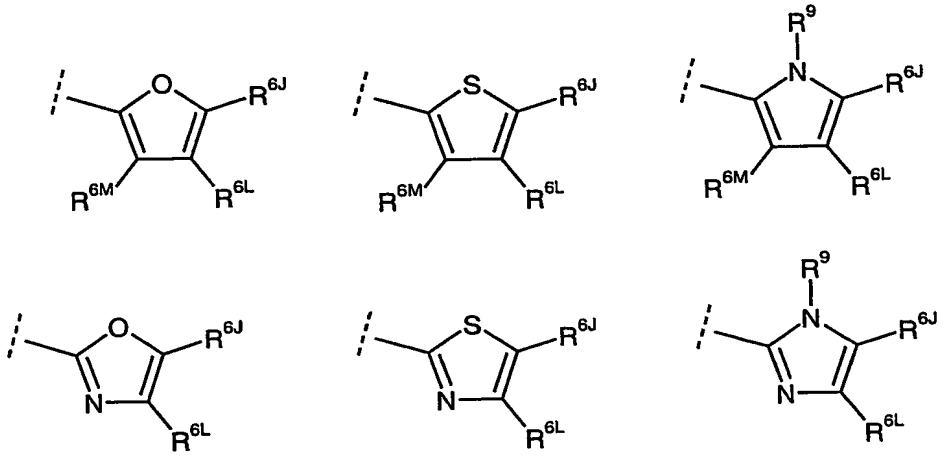
Preferably, in sub-formula (z), no more than two (for example no more than one) of J, L, M and Q are nitrogen (N).

Suitably, Q is C-[connection point to formula (I)].

Suitably, R^9 is a hydrogen atom (H) or methyl.

Suitably, R^{6J}, R^{6L}, R^{6M} and/or R^{6Q} independently is or are: a hydrogen atom (H); fluoro; chloro; C_{1-2}alkyl (e.g. methyl); C_1fluoroalkyl (e.g. CF_3); C_{1-2}alkoxy (methoxy); C_1fluoroalkoxy (e.g. CF_2HO-); OH (including any tautomer thereof); or phenyl optionally substituted by one substituent being fluoro, methyl, C_1fluoroalkyl, methoxy or C_1fluoroalkoxy. More SuitablyR^{6J}, R^{6L}, R^{6M} and/or R^{6Q} independently is or are H, OH (including any keto tautomer thereof), or more preferably C_{1-2}alkyl (e.g. methyl) or C_1fluoroalkyl.

When Ar has the sub-formula (z), then sub-formula (z) can suitably be one of the following:



Suitably, R^{7a} is H or C_{1-2}alkyl, more suitably H or methyl. Suitably, R^{8a} is H.

Preferably, R^7 and/or R^8 are independently a hydrogen atom (H); C_{1-2}alkyl such as methyl; C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two (e.g. one) substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or R^7 and R^8 together are -$(CH_2)_n{}^6$- or -$(CH_2)_n{}^8$-X^7-$(CH_2)_n{}^9$- wherein X^7 is NR^{14} or preferably O.

When R^7 is cycloalkyl or optionally substituted phenyl, then preferably R^8 is neither cycloalkyl nor optionally substituted phenyl. In this case, R^8 can for example be H.

More preferably, R^7 and/or R^8 independently are a hydrogen atom (H) or C_{1-2}alkyl. It is preferable that R^8 is a hydrogen atom (H).

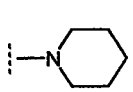
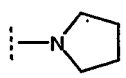
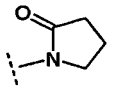
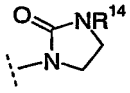
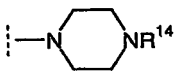
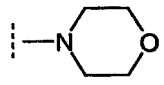
Preferably n^6 is 4 or 5. Preferably n^7 is 3 or 4. Preferably, n^8, n^9 and/or n^{10} independently is/are 2.

Preferably, R^{12} and/or R^{13} independently are H; C_{1-2}alkyl such as methyl; C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two (e.g. one) substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or R^{12} and R^{13} together are $-(CH_2)_n{}^{6a}-$ or $-(CH_2)_n{}^{8a}-X^{12}-(CH_2)_n{}^{9a}-$ in which X^{12} is NR^{14a} or preferably O.

When R^{12} is cycloalkyl or optionally substituted phenyl, then preferably R^{13} is neither cycloalkyl nor optionally substituted phenyl. In this case, R^{13} can for example be H.

More preferably, R^{12} and/or R^{13} independently are a hydrogen atom (H) or C_{1-2}alkyl. It is preferable that R^{13} is a hydrogen atom (H).

Preferably n^{6a} is 4 or 5. Preferably n^{7a} is 3 or 4. Preferably, n^{8a}, n^{9a} and/or n^{10a} independently is/are 2.

In one embodiment of the invention, NR^7R^8 and/or $NR^{12}R^{13}$ can for example independently be  or  or  or  , or  (i.e. R^{12} and R^{13} together or R^7 and R^8 together are $-(CH_2)_2-N(R^{14})-(CH_2)_2-$), or  (i.e. R^{12} and R^{13} together or R^7 and R^8 together are $-(CH_2)_2-O-(CH_2)_2-$), or NMe_2.

Suitably, R^{14}, R^{14a}, R^{17} and/or R^{17a} independently are: a hydrogen atom (H); C_{1-2}alkyl; C_1fluoroalkyl (e.g. CF_3); -C(O)Me; $-C(O)NH_2$; or $-S(O)_2Me$. More suitably, R^{14}, R^{14a}, R^{17} and/or R^{17a} independently is/are: H, C_{1-2}alkyl, or -C(O)Me; or for example H or C_{1-2}alkyl.

Suitably, R^{15} is a hydrogen atom (H) or C_{1-4}alkyl (e.g. ^{t}Bu or C_{1-2}alkyl e.g. methyl); more suitably, R^{15} is a hydrogen atom (H).

Where R^{15a}, independent of other R^{15a}, is a hydrogen atom (H) or C_{1-4}alkyl, it can for example be H, ^{t}Bu or C_{1-2}alkyl such as methyl. Suitably, R^{15a}, independent of other R^{15a}, is H or C_{1-2}alkyl, more preferably H.

Preferably, R^{15b} is H.

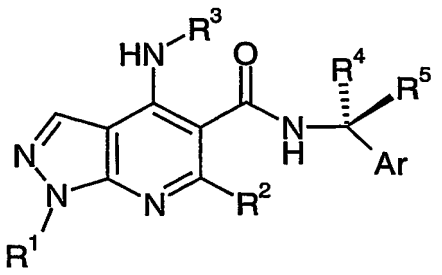
Suitably, R^{16} is C_{1-4}alkyl (e.g. C_{1-2}alkyl) or C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl); more suitably R^{16} is C_{1-4}alkyl (e.g. C_{1-2}alkyl).

Preferably, R^{16a} is:
C_{1-4}alkyl (e.g. C_{1-2}alkyl);
C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl) optionally substituted by one oxo (=O), OH or methyl substituent (e.g. optionally substituted at the 3- or 4-position of a C_{5-6}cycloalkyl ring; and/or preferably unsubstituted C_{3-6}cycloalkyl);
C_{3-6}cycloalkyl-CH_2- (e.g. C_{5-6}cycloalkyl-CH_2-);
pyridinyl (e.g. pyridin-2-yl) optionally substituted on a ring carbon atom by one of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;
Ar^{5c};
phenyl optionally substituted by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;
benzyl optionally substituted on its ring by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or
a 5- or 6-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR^{27} where R^{27} is H, C_{1-2}alkyl or -C(O)Me (preferably H or C_{1-2}alkyl); and wherein the ring is not substituted at carbon.

More preferably, R^{16a} is: C_{1-4}alkyl (e.g. C_{1-2}alkyl); unsubstituted C_{3-6}cycloalkyl (e.g. unsubstituted C_{5-6}cycloalkyl); phenyl optionally substituted by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or benzyl optionally substituted on its ring by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy.

Suitably, R^{30}, independent of other R^{30}, is a hydrogen atom (H) or C_{1-4}alkyl, for example H, t-butyl or C_{1-2}alkyl.

Preferably, the compound of formula (I) or the salt thereof is a compound of formula (IA) or a salt thereof:



(IA)

Formula (IA) means that more than 50% of the compound or salt present has the stereochemistry shown at the carbon atom bearing the R^4 and R^5 groups.

Preferably, the stereochemistry at the carbon atom bearing the R^4 and R^5 groups is such that there is an enantiomeric excess (e.e.) of 50% or more at the carbon atom bearing the R^4 and R^5 groups (ignoring the stereochemistry at any other carbon atoms). More preferably, the enantiomeric excess (e.e.) is 70% or more or 80% or more, still more preferably 90% or more, yet more preferably 95% or more, at the carbon atom bearing the R^4 and R^5 groups (ignoring the stereochemistry at any other carbon atoms).

"Enantiomeric excess" (e.e.) is defined as the percentage of the major isomer present minus the percentage of the minor isomer present. For example, if 95% of major isomer is present and 5% of the minor isomer is present, then the e.e. would be 90%.

In formula (IA), it is preferable that R^4 is not a hydrogen atom (H). In formula (IA), more preferably R^4 is methyl, ethyl, C_1fluoroalkyl (such as CF_3), -CH_2OH, or -CH_2OMe; still more preferably R^4 is methyl, ethyl, CF_3 or -CH_2OH; yet more preferably R^4 is methyl or ethyl; and most preferably R^4 is ethyl.

In formula (IA), it is particularly preferable that R^5 is a hydrogen atom (H) and R^4 is not a hydrogen atom (H). In formula (IA), it is more preferable that R^5 is a hydrogen atom (H); and R^4 is methyl, ethyl, C_1fluoroalkyl (such as CF_3), -CH_2OH, or -CH_2OMe (e.g. methyl, ethyl, CF_3 or -CH_2OH). In formula (IA), it is most preferable that R^5 is a hydrogen atom (H); and R^4 is methyl or ethyl (preferably ethyl).

In formula (IA), when R^4 is not a hydrogen atom (H), and optionally when R^5 is a hydrogen atom (H), it is particularly preferable that Ar, such as having sub-formula (x1), is a monocycle. That is, in formula (IA) and when R^4 is not a hydrogen atom (H), it is particularly preferable that two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are not taken together to form part of a second ring.

The Examples 1, 8, 24, 28, 63, 127, 129, 174, and 178 disclosed herein, having the formula (IA) wherein R^5 is H, and wherein R^4 is methyl, ethyl, $-CH_2OH$, or $-CH_2OMe$, and wherein Ar is a monocycle, have been found to have greater PDE4B inhibitory activity than the comparable Examples 6, 7, 29, 26, 64, 126, 124, 170, and 177 which have the opposite stereochemistry at the CR^4R^5 carbon atom.

In an especially preferable embodiment, N-CR^4R^5-Ar is the N-CR^4R^5-Ar group as defined in any one of Examples 1 to 314.

It is particularly preferred that the compound of formula (I) or the salt thereof is:

1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-methyl-1-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(diphenylmethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(3-pyridinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-methyl-1-(4-pyridinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(3-hydroxy-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[2-(dimethylamino)-1-phenylethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-phenyl-2-(1-pyrrolidinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(hydroxymethyl)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(propyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

methyl 3-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-phenylpropanoate

1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

ethyl ({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)(phenyl)acetate

1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*S*)-2-(methyloxy)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[(1*R*)-2-amino-2-oxo-1-phenylethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*R*)-2-(methyloxy)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-(2-hydroxy-1,1-diphenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-cyanophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[cyano(phenyl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-{cyclopropyl[4-(methyloxy)phenyl]methyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-(1,2-diphenylethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(methyloxy)phenyl]butyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(aminocarbonyl)-1-phenylpropyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-phenylcyclopentyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(4-phenyltetrahydro-2*H*-pyran-4-yl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-phenylcyclopropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(cyclohexyloxy)-3-methylphenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[3-(cyclohexyloxy)-4-(methyloxy)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(cyclohexyloxy)-3-hydroxyphenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(cyclopentyloxy)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(1,1-dimethylethyl)phenyl]cycloheptyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-1-(4-iodophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(aminosulfonyl)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-methyl-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(1,3-benzodioxol-5-yl)cyclohexyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(methyloxy)phenyl]cyclohexyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)cyclohexyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chlorophenyl)cyclopentyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2-chlorophenyl)cyclopentyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-{1-[4-(1,1-dimethylethyl)phenyl]cyclohexyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{(1*S*)-1-[4-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-(1-phenylhexyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-(1-phenylpentyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-(2-methyl-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-(1-phenylbutyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(2,2,2-trifluoro-1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[cyclopropyl(phenyl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-(1-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3,4-dichlorophenyl)-2-hydroxyethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-methylphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(2-methylphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-bromophenyl)-2,2,2-trifluoroethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-(diphenylmethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

ethyl ({[4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)(phenyl)acetate

N-[1-(4-chlorophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-(1-methyl-1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-(1,2-diphenylethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

methyl 3-({[4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-phenylpropanoate

4-(cyclohexylamino)-1-ethyl-*N*-[1-(hydroxymethyl)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-(3-hydroxy-1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-phenyl-2-(1-pyrrolidinyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[2-(dimethylamino)-1-phenylethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-2-(methyloxy)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[(1*R*)-2-amino-2-oxo-1-phenylethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-2-(methyloxy)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-1-(1-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[phenyl(4-phenyl-1,3-thiazol-2-yl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[cyano(phenyl)methyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(1-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-(2-hydroxy-1,1-diphenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[(1*R*)-1-(4-bromophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-bromophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-[1-(2-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chloro-2-fluorophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chloro-4-methylphenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chloro-2-fluorophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chloro-4-methylphenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)-2-hydroxyethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-*N*-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*S*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-[(1-acetyl-4-piperidinyl)amino]-*N*-(diphenylmethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*S*)-1-(4-nitrophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-(1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

(2*R*)-[({1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl}carbonyl)amino][3-(methyloxy)phenyl]ethanoic acid

1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(2-methylphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-bromophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(4-methylphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-bromophenyl)-2,2,2-trifluoroethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[3-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(4-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(2-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(2-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(3-hydroxyphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(3-hydroxyphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[(1*S*,3*R*)- and (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Isomer 1)
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Isomer 2)
N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)ethyl]-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Diastereoisomer 1)

1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Diastereoisomer 2)

N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2) hydrochloride

4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, or
4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

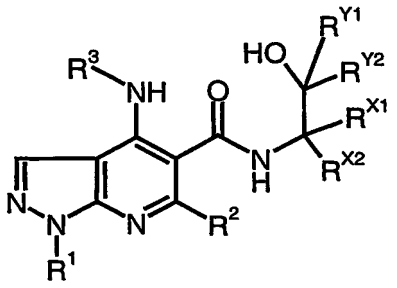
as a compound **or** a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

The structures of these specific compounds are given in Examples 1 to 314 hereinafter.

It is particularly preferred that the compound of formula (I) or the salt thereof is one of Examples 1 to 314, as a compound or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. The structures of these specific compounds are given in Examples 1 to 314 hereinafter, and their names are given in the Examples section.

In one embodiment, is still further preferred that the compound of formula (I) or the salt thereof is a compound of Example 73, 98, 283, 304, 306, 307, 310 or 311, as defined by the structures and/or names described herein, or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. The structures and names of these Examples are described in the Examples section. These Examples are thought to be suitable for inhaled administration.

According to one optional embodiment of the invention, the compound of formula (I) or salt thereof can be a compound of Formula (XXVIII) or a salt thereof:



(XXVIII)

wherein:

R^{X1} is a hydrogen atom (H), C_{1-2}alkyl or C_1fluoroalkyl (preferably H);

R^{Y1} is a hydrogen atom (H) or C_{1-2}alkyl;

R^{Y2} is a hydrogen atom (H); C_{1-3}alkyl (e.g. C_{1-2}alkyl or methyl); or $-(CH_2)_n{}^{7aa}$-OH; wherein n^{7aa} is 1, 2 or 3;

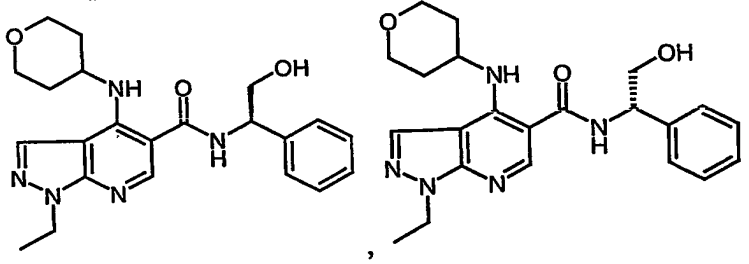
and

R^{X2} is Ar^A, wherein:

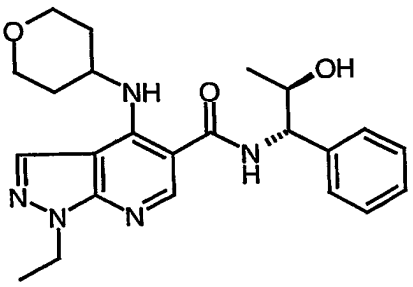
(i) Ar^A is phenyl optionally substituted by one or two substituents independently being: fluoro, chloro, bromo, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy; OH; $-NR^{11aa}R^{11bb}$ (wherein R^{11aa} is H or C_{1-2}alkyl and R^{11bb} is H, C_{1-2}alkyl, $-C(O)-C_{1-2}$alkyl or $-S(O)_2-C_{1-2}$alkyl); cyano; $-C(O)-NR^{11cc}R^{11dd}$ (wherein R^{11cc} and R^{11dd} independently are H or C_{1-2}alkyl); $-C(O)-OR^{11ee}$ wherein R^{11ee} is H or C_{1-2}alkyl; or $-S(O)_2-R^{11ff}$ (wherein R^{11ff} is C_{1-2}alkyl, NH_2, NHMe or NMe_2); or the phenyl Ar^A is optionally substituted at two adjacent Ar ring atoms by the two ends of a chain which is: $-(CH_2)_4-$, $-(CH_2)_3-$, or -CH=CH-CH=CH-; or

(ii) Ar^A is an optionally substituted 5-membered heterocyclic aromatic ring containing 1, 2, 3 or 4 heteroatoms (e.g. 1, 2 or 3 heteroatoms) selected from O, N or S; and wherein when the heterocyclic aromatic ring Ar^A contains 2, 3 or 4 heteroatoms (e.g. 2 or 3 heteroatoms), one is selected from O, N and S and the remaining heteroatom(s) are N; and wherein the heterocyclic aromatic ring Ar^A is optionally substituted by one or two groups independently being C_{1-4}alkyl (e.g. C_{1-2}alkyl) or OH (including any keto tautomer of an OH-substituted aromatic ring).

A compound of formula (XXVIII) can suitably be:



, or



These three compounds are:

1-Ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,

1-Ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide, and
1-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide.

These three compounds are disclosed as Intermediates 42, 43 and 46 respectively in copending international patent application PCT/EP2003/014867 (=PCT/EP03/14867), filed on 19 December 2003 in the name of Glaxo Group Limited, the content of which is incorporated herein by reference. The compounds of Formula (XXVIII) are also disclosed in PCT/EP2003/014867 and are incorporated herein by reference.

Salts, solvates, isomers, tautomeric forms, molecular weights, etc.

Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable. Suitable pharmaceutically acceptable salts can include acid or base addition salts.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamaic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, formate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2- naphthalenesulfonate) or hexanoate salt.

A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base (e.g. triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine), optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration.

Other suitable pharmaceutically acceptable salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as sodium, potassium, calcium or magnesium salts; in particular pharmaceutically acceptable metal salts of one or more carboxylic acid moieties that may be present in the the compound of formula (I).

Other non-pharmaceutically acceptable salts, eg. oxalates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

Also included within the scope of the invention are all solvates, hydrates and complexes of compounds and salts of the invention.

Certain groups, substituents, compounds or salts included in the present invention may be present as isomers. The present invention includes within its scope all such isomers, including racemates, enantiomers and mixtures thereof.

In the compounds or salts, pharmaceutical compositions, uses, methods of treatment/prophylaxis, methods of preparing, etc. according to the present invention, where a defined isomeric configuration e.g. stereochemical configuration is described or claimed, the invention includes a mixture comprising (a) a major component of the compound or salt which is in the described or claimed configuration, together with (b) one or more minor components of the compound or salt which is/are not in the described or claimed configuration. Preferably, in such a mixture, the major component of the compound or salt which is in the described or claimed configuration represents 70% or more, or 75% or more, more preferably 85% or more, still more preferably 90% or more, yet more preferably 95% or more, yet more preferably 98% or more, of the total amount of compound or salt present in the mixture on a molarity basis.

The percentage of one isomeric / stereochemical component in a mixture of different isomeric / stereochemical components, and if appropriate enantiomeric and/or diastereomeric excesses, can be measured using techniques known in the art. Such methods include the following:

(1) Measurement using NMR (e.g. ^{1}H NMR) spectroscopy in the presence of chiral agent. One can measure a nuclear magnetic resonance (NMR) spectrum (preferably a ^{1}H NMR spectrum, and/or a solution-phase NMR spectrum e.g. in $CDCl_3$ or D6-DMSO solvent) of the compound/salt mixture in the presence of a suitable chiral agent which "splits" the NMR peaks of a given atom in different isomers into different peak positions. The chiral agent can be: i) an optically pure reagent which reacts with the compound/salt e.g. to form a mixture of diastereomers, ii) a chiral solvent, iii) a chiral molecule which forms a transient species (e.g. diastereomeric species) with the compound/salt, or iv) a chiral shift reagent. See e.g. J. March, "Advanced Organic Chemistry", 4th edn., 1992, pages 125-126 and refs. 138-146 cited therein. A chiral shift reagent can be a chiral lanthanide shift reagent such as tris[3-trifluoroacetyl-*d*-camphorato]europium-(III) or others as described in Morrill, "Lanthanide Shift Reagents in Stereochemical Analysis", VCH, New York, 1986. Whatever the chiral agent is that is used, usually, the relative integrals (intensities) for the NMR peaks of a given atom or group in different isomers can provide a measurement of the relative amounts of each isomer present.

(2) Measurement using chiral chromatography, especially on an analytical scale. A suitable chiral column which separates the different isomeric components can be used to effect separation, e.g. using gas or liquid chromatography such as HPLC, and/or e.g. on an analytical scale. The peaks for each isomer can be integrated (area under each peak); and a comparison or ratio of the integrals for the different isomers present can give a measurement of the percentage of each isomeric component present. See for example: "Chiral Chromatography", Separation Science Series Author: T.E. Beesley and R.P.W. Scott, John Wiley & Sons, Ltd., Chichester, UK, 1998, electronic Book ISBN: 0585352690, Book ISBN: 0471974277.

(3) Separation of pre-existing diastereomeric mixtures which are compounds/salts of the invention can be achieved (usually directly, without derivatisation) using separation techniques such as gas or liquid chromatography. Diastereomeric ratios and/or excesses can thereby be derived e.g. from the relative peak areas or relative separated masses.

(4) Conversion with a chiral / optically-active agent and subsequent separation of the resulting isomers, e.g. diastereomers. Conversion can be via derivatisation of a derivatisable group (e.g. -OH, -NHR) on the compound/salt with an optically-active derivatising group (e.g. optically active acid chloride or acid anhydride); or can be via formation of an acid or base addition salt of the compound by treatment of the compound with an optically-active acid or base, such as + or – di-para-toluoyl tartaric acid. After derivatisation, separation of the resulting isomers e.g. diastereomers, can be using gas or liquid chromatography (usually non-chiral); or (especially with isomeric salts) can be by selective crystallisation of a single isomeric e.g. diastereoisomeric salt. Determination of isomeric ratios and/or excesses can be using chromatography peak areas or measurement of mass of each separated isomer.

See e.g. J. March, "Advanced Organic Chemistry", 4th edn., 1992, pages 120-121 and 126, and refs. 105-115 and 147-149 cited therein.

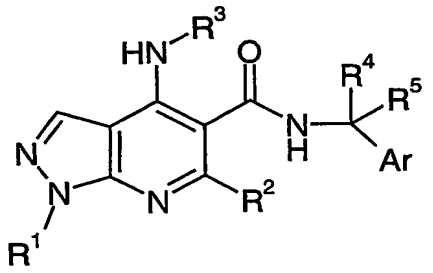
(5) Measurement of optical activity [alpha] of mixture and comparison with optical activity of pure isomer $[alpha]_{max}$ if available (e.g. see J. March, "Advanced Organic Chemistry", 4th edn., 1992, page 125 and refs. 138-139 cited therein). This assumes a substantially linear relationship between [alpha] and concentration.

Certain of the groups, e.g. heteroaromatic ring systems, included in compounds of formula (I) or their salts may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures.

Especially when intended for oral medicinal use, the compound of formula (I) can optionally have a molecular weight of 1000 or less, for example 800 or less, in particular 650 or less or 600 or less. Molecular weight here refers to that of the unsolvated "free base" compound, that is excluding any molecular weight contributed by any addition salts, solvent (e.g. water) molecules, etc.

Synthetic Process Routes

The following processes can be used to make the compounds of the invention:

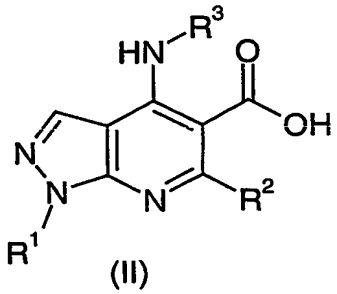


(I)

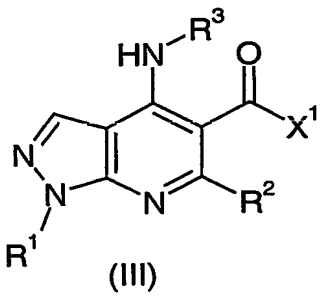
Some of the following synthetic processes may be exemplified for compounds of Formula (I) wherein R^2 is a hydrogen atom (H). However, some or all of these processes can also be used with appropriate modification, e.g. of starting materials and reagents, for making compounds of Formula (I) wherein R^2 is methyl.

Process A

To form a compound of formula (I), a carboxylic acid of formula (II) can be converted into an activated compound of formula (III) wherein X^1 is a leaving group substitutable by an amine (as defined below), and subsequently the activated compound can be reacted with an amine of formula $ArCR^4R^5NH_2$:

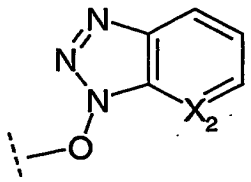


(II)



(III)

For example, the activated compound (the compound of formula (III)) can be the acid chloride (X^1 = Cl). This can be formed from the carboxylic acid of formula (II) e.g. by reaction with thionyl chloride, either in an organic solvent such as chloroform or without solvent. Alternatively, the activated compound (the compound of formula (III)) can be an activated ester wherein the leaving group X^1 is



X_2 = CH or N

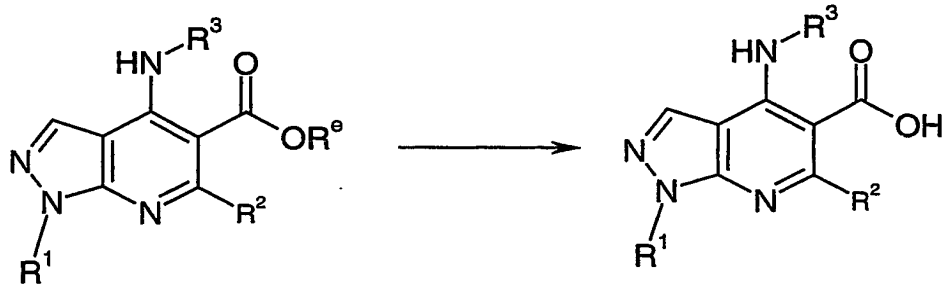
The latter activated compound of formula (III) can be formed from the carboxylic acid of formula (II) either:

(a) by reaction of the carboxylic acid with a carbodiimide such as EDC, which is 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide and is also 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or a salt thereof e.g. hydrochloride salt,
preferably followed by reaction of the resulting product with 1-hydroxybenzotriazole (HOBT); reaction (a) usually being carried out in the presence of a solvent (preferably anhydrous) such as dimethyl formamide (DMF) or acetonitrile and/or preferably under anhydrous conditions and/or usually at room temperature (e.g. about 20 to about 25 °C);

or:

(b) by reaction with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) ,in the presence of a base such as diisopropylethylamine ($^iPr_2NEt$ = DIPEA), and usually in the presence of a solvent such as dimethyl formamide (DMF) or acetonitrile and/or preferably under anhydrous conditions and/or usually at room temperature (e.g. about 20 to about 25 °C).

Compounds of formula (II) can be prepared by hydrolysis of an compound of formula (IV), an ester:



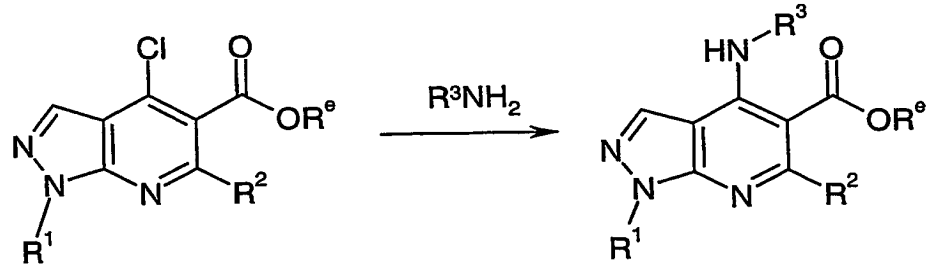
(IV) (II)

This process preferably involves reaction of compound of formula (IV) with either:

(a) a base, such as sodium hydroxide or potassium hydroxide, in a solvent, e.g. an aqueous solvent such as aqueous ethanol or aqueous dioxane or

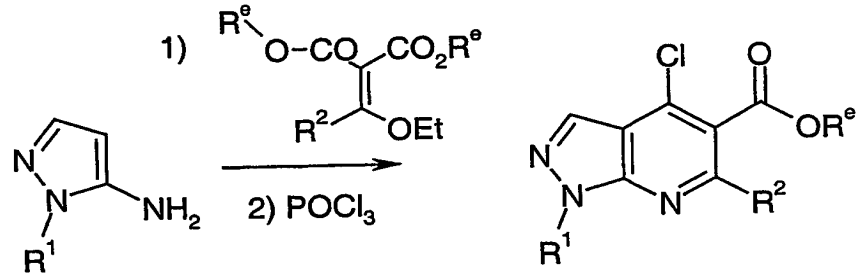
(b) an acid, such as hydrochloric acid, in a solvent, e.g. an aqueous solvent such as aqueous dioxane.

Compounds of formula (IV) can be prepared according to a method, for example as described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027, by reaction of a compound of formula (V) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane or acetonitrile. The reaction may require heating e.g. to ca. 60-100°C, for example ca. 80-90°C:



(V) (IV)

Compounds of formula (V) are also described in the above reference. They can be prepared by reaction of a compound of formula (VI) with $(R^2)(OEt)C{=}C(CO_2R^e)_2$, which can for example be diethyl(ethoxymethylene)malonate (wherein R^2 is H and R^e is Et) or diethyl 2-(1-ethoxyethylidene)malonate (wherein R^2 is Me and R^e is Et), with heating, followed by reaction with phosphorous oxychloride, again with heating:

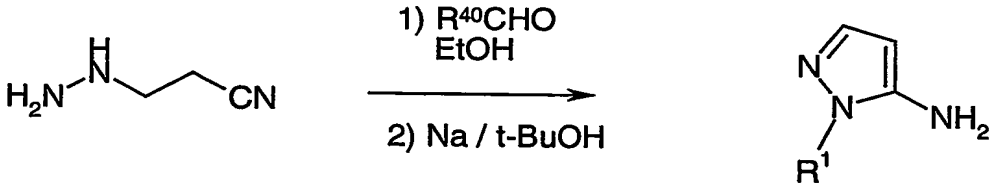


(VI) (V)

For examples of the compound (VI) to compound (V) process, see for example: (i) the Intermediate 1 synthesis and G. Yu et. al., *J. Med Chem.*, 2001, 44, 1025-1027 hereinafter, where R^2 = H and R^1 = ethyl; and see (ii) the Intermediate 10 synthesis hereinafter where R^2 = Me and R^1 = ethyl; and see (iii) Intermediate 122 synthesis

hereinafter wherein R^2 = H and R^1 = methyl (i.e. reaction of 5-amino-1-methyl pyrazole with diethylethoxymethylene malonate).

Where the desired amino pyrazole of formula (VI) is not commercially available, preparation of the amino pyrazole (VI) can be achieved, for example, using methods described by Dorgan et. al. in *J. Chem. Soc., Perkin Trans. 1*, (4), 938-42; 1980, by reaction of cyanoethyl hydrazine with a suitable aldehyde of formula $R^{40}CHO$ in a solvent such as ethanol, with heating, followed by reduction, for example reduction with sodium in a solvent such as t-butanol. R^{40} should be chosen so as to contain one less carbon atom than R^1, for example R^{40} = methyl will afford R^1 = ethyl.

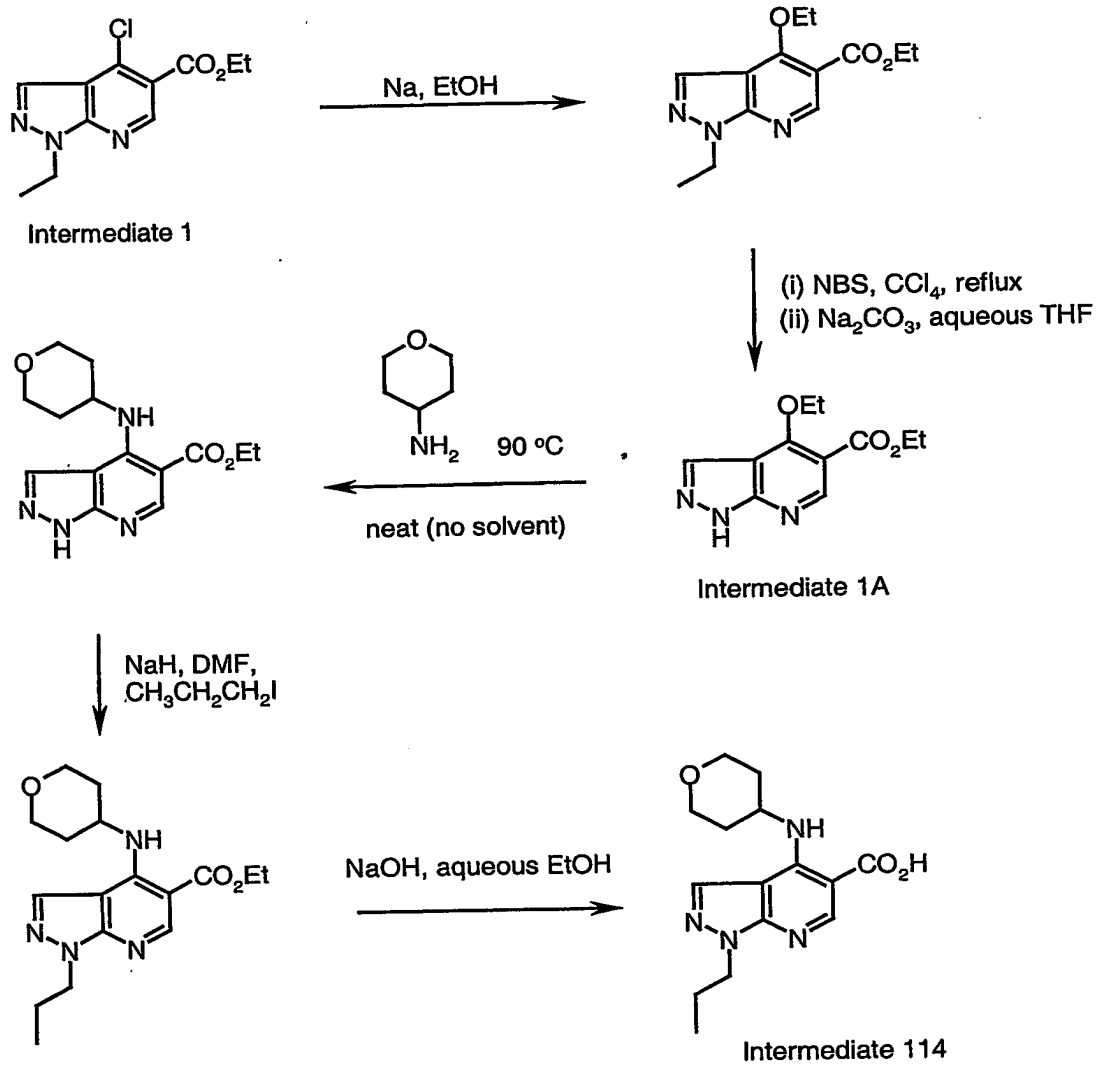


(VI)

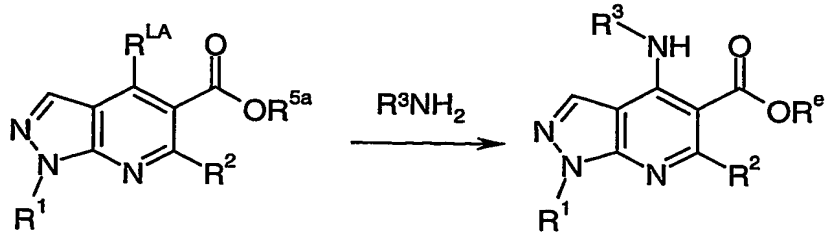
Alternatively, e.g. where the desired amino pyrazole of Formula (VI) is not commercially available, preparation of the 4-amino 5-ester/acid compounds of Formulae (IV) and (II) can be achieved from a (different R^1) 4-chloro 5-ester compound of Formula (V) (e.g. Intermediate 1, wherein R^1 = ethyl), using a generalised version of the reaction scheme shown in Intermediate 114 and shown below. In this method:

- the 4-chloro 5-ester pyrazolopyridine of Formula (V) (e.g. Intermediate 1) is optionally converted to the 4-alkoxy (e.g. C_{1-4}alkoxy such as ethoxy) pyrazolopyridine;
- the R^1 group is removed (e.g. using N-bromosuccinimide (NBS) and preferably base e.g. Na_2CO_3) (e.g. to give Intermediate 1A – an alternative synthesis for which is given under "Intermediate 1A" hereinafter);
- the 4-amino NHR^3 group is inserted by displacing the 4-chloro or 4-alkoxy group by reaction with R^3NH_2;
- and the pyrazolopyridine is alkylated at N-1 by reacting it with R^1-X^{41} where X^{41} is a group displaceable by the N-1 nitrogen of the pyrazolopyridine in order to re-insert the desired R^1 group. X^{41} can for example be a halogen, e.g. Cl, Br or I; or X^{41} can be -O-SO_2-R^{41} where R^{41} is C_{1-4}alkyl, C_{1-2}fluoroalkyl, or phenyl optionally substituted by C_{1-2}alkyl.

The scheme below (Intermediate 114 scheme) shows a suitable route and conditions for this, to insert R^1 = n-propyl:

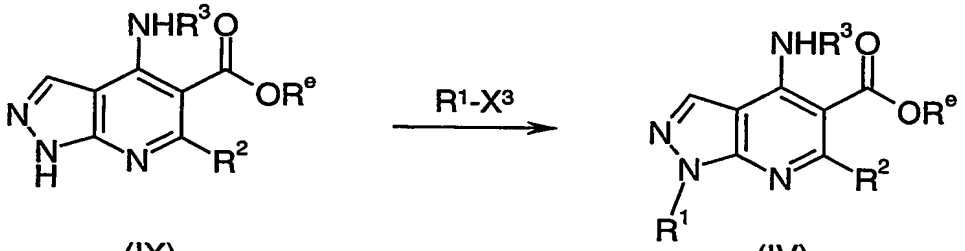


In an alternative embodiment of Process A, the 4-chloro substituent in the compound of formula (V) can be replaced by another halogen atom, such as a bromine atom, or by another suitable leaving group which is displaceable by an amine of formula R^3NH_2. The leaving group displaceable by the amine can for example be R^{LA}, in a compound of formula (Va), wherein R^{LA} is an alkoxy group OR^{35} such as OC_{1-4}alkyl (in particular OEt) or a group -O-S(O)$_2$-R^{37}, wherein R^{37} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction of the compound of formula (Va) with the amine of formula R^3NH_2 may be carried out with or without solvent and may require heating:



(Va) (IV)

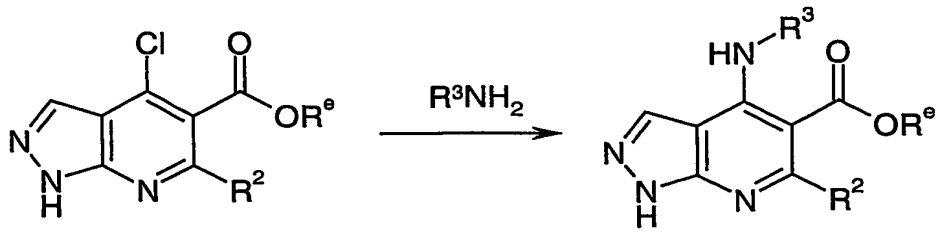
In another alternative embodiment of Process A, the compound of formula (IV), described herein, can be prepared by reaction of a compound of formula (IX) with an alkylating agent of formula R^1-X^3, where X^3 is a leaving group displaceable by the 1-position pyrazolopyridine nitrogen atom of the compound of formula (IX):



(IX) (IV)

A suitable alkylating agent of formula R^1-X^3 can be used. For example, X^3 can be a halogen atom such as a chlorine atom or more preferably a bromine or iodine atom, or X^3 can be –O-S(O)$_2$-R^{36} wherein R^{36} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction is preferably carried out in the presence of a base; the base can for example comprise or be potassium carbonate, sodium carbonate, sodium hydride, potassium hydride, or a basic resin or polymer such as polymer-bound 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine. The reaction is preferably carried out in the presence of a solvent, e.g. an organic solvent such as DMF; the solvent is preferably anhydrous.

Compounds of formula (IX) can be prepared, using a method analogous to that used for the preparation of compounds of formula (IV) from compounds of formula (V), by reaction of a compound of formula (X) (which is the same as compound of formula (V) but wherein R^1 = H) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane or acetonitrile. The reaction may require heating e.g. to ca. 60-100°C, for example ca. 80-90°C:

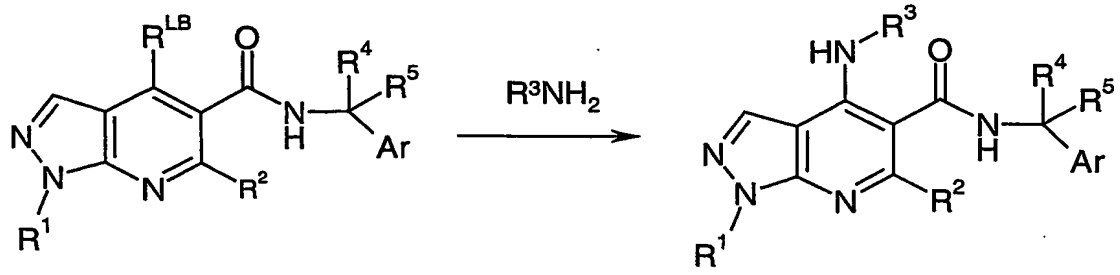


(V) (IX)

Compound of formula (V) can be made as dewcribed above.

Process B

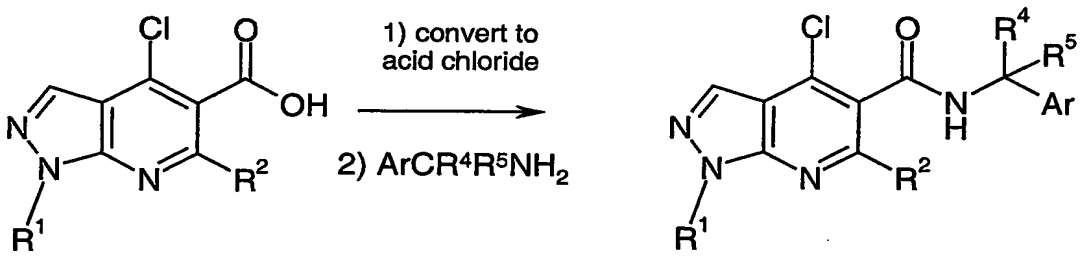
Compounds of formula (I) can be prepared by reaction of a compound of formula (VII) with an amine of formula R^3NH_2. In the compound of formula (VII), R^{LB} is a leaving group which is displaceable by the amine of formula R^3NH_2. R^{LB} can preferably be a bromine atom (Br) or more preferably a chlorine atom (Cl), or alternatively R^{LB} can be an alkoxy group OR^{35} such as OC_{1-4}alkyl (in particular OEt) or a group -O-S(O)$_2$-R^{37}, wherein R^{37} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction of (VII) to (I) is preferably carried out in the presence of a base, such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, THF, dioxane or acetonitrile. The reaction may require heating, e.g. to ca. 60-100 °C or ca. 80-90 °C, for example for 8-48 or 12-24 hours:



(VII) (I)

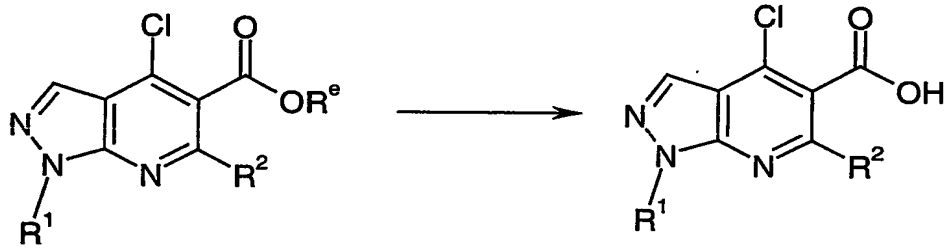
Compounds of formula (VII), wherein R^{LB} is a chlorine atom (compound of formula (VIIa), can be prepared in a two step procedure as described by Bare et. al. in *J. Med.*

Chem. 1989, 32, 2561-2573. This process involves 2 steps. In the first step, a compound of formula (VIII) is reacted with thionyl chloride (or another agent suitable for forming an acid chloride from a carboxylic acid), either in an organic solvent such as chloroform or THF, or as a neat solution. This reaction may require heating and the thus-formed intermediate may or may not be isolated. Step two involves reaction with an amine of formula $ArCR^4R^5NH_2$, in an organic solvent such as THF or chloroform and may also involve the use of a base such as triethylamine or diisopropylethylamine:



(VIII) (VIIa)

Compounds of formula (VIII) can be prepared by hydrolysis of an ester of formula (V) according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027. This procedure preferably involves reaction with a base, such as sodium hydroxide or potassium hydroxide, in a solvent e.g. an aqueous solvent such as aqueous ethanol or aqueous dioxane:

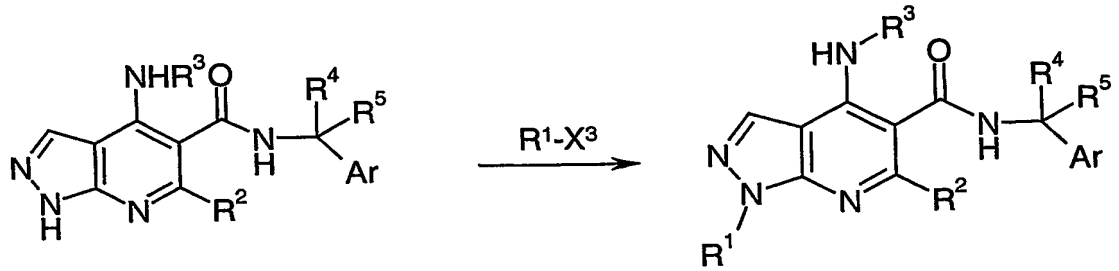


(V) (VIII)

Compounds of formula (V) can be prepared as described in Process A above.

Process C

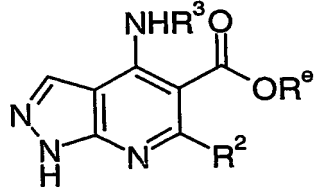
A compounds of formula (I) can be prepared by reaction of a compound of formula (IXa) with an alkylating agent of formula R^1-X^3, where X^3 is a leaving group displaceable by the 1-position pyrazolopyridine nitrogen atom of the compound of formula (IXa):



(IXa) (I)

A suitable alkylating agent of formula R^1-X^3 can be used. For example, X^3 can be a halogen atom such as a chlorine atom or more preferably a bromine or iodine atom, or X^3 can be –O-S(O)$_2$-R^{36} wherein R^{36} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction is preferably carried out in the presence of a base; the base can for example comprise or be potassium carbonate, sodium carbonate, sodium hydride, potassium hydride, or a basic resin or polymer such as polymer-bound 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine. The reaction is preferably carried out in the presence of a solvent, e.g. an organic solvent such as DMF; the solvent is preferably anhydrous.

Compounds of formula (IXa) can be prepared from a compound of formula (IX):



(IX)

by hydrolysis of the ester and conversion of the resulting carboxylic acid to the amide of formula (IXa) by activation of the acid and reaction with an amine of formula $ArCR^4R^5NH_2$. The ester (IX) to acid to amide (IXa) conversion can suitably use the reagents and reaction conditions mentioned in Process A above for conversion of (IV) to (II) to (III) to (I).

The ester compound of formula (IX) can be prepared using the method described in the alternative embodiment of Process A, above.

Process D: *Conversion of one compound of formula (I), (II) or (IV) or salt thereof into another compound of formula (I), (II) or (IV) or salt thereof*

One compound of formula (I), (II) or (IV) or salt thereof can be converted into another compound of formula (I), (II) or (IV) or salt thereof. This conversion preferably comprises or is one or more of the following processes D1 to D7:

D1. Conversion of a ketone into the corresponding oxime (e.g. Examples 231-281).

D2. An oxidation process. For example, the oxidation process can comprise or be oxidation of an alcohol to a ketone (e.g. using Jones reagent) or oxidation of an alcohol or a ketone to a carboxylic acid. The oxidation process can e.g. comprise or be conversion of a nitrogen-containing compound of formula (I) or salt thereof to the corresponding N-oxide (e.g. using *meta*-chloroperoxybenzoic acid), for example conversion of a pyridine-containing compound to the corresponding pyridine N-oxide (e.g. see Examples 210-212 of PCT/EP03/11814, filed on 12 September 2003 and incorporated herein by reference, for suitable process details).

D3. A reduction process, for example reduction of a ketone or a carboxylic acid to an alcohol.

D4. Acylation, for example acylation of an amine (e.g. see Examples 329-349 and Example 353 of PCT/EP03/11814, filed on 12 September 2003 and incorporated herein by reference, for suitable process details), or acylation of a hydroxy group.

D5. Alkylation, for example alkylation of an amine or of a hydroxy group.

D6. Hydrolysis, e.g. hydrolysis of an ester to the corresponding carboxylic acid or salt thereof (e.g. see Examples 351, 488, 489, 650, 651 of PCT/EP03/11814, filed on 12 September 2003 and incorporated herein by reference, for suitable process details).

D7. Deprotection, e.g. deprotection (e.g. deacylation or t-butyloxycarbonyl (BOC) removal) of an amine group.

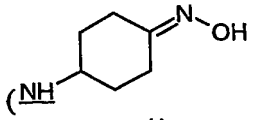
D8. Formation of an ester or amide, for example from the corresponding carboxylic acid.

D9. Sulfonylation, e.g. sulfonamide formation by reaction of an amine with a sulfonyl halide e.g. a sulfonyl chloride (e.g. see Examples 322-328 of PCT/EP03/11814, filed on 12 September 2003 and incorporated herein by reference, for suitable process details).

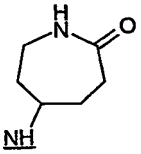
and/or

D10. Beckmann rearrangement of one compound of formula (I) into another compound of formula (I), preferably using cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) together

with a formamide such as DMF, e.g. at room temperature (see L.D. Luca, *J. Org. Chem.*, 2002, 67, 6272-6274). The Beckmann rearrangement can for example comprise conversion of a compound of formula (I) wherein NHR^3 is of sub-formula (o2)

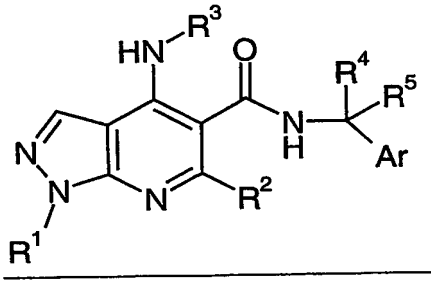


) into a compound of formula (I) wherein NHR^3 is of sub-formula



(m3) ( ), and suitable process details can be as illustrated in Examples 658 and 659 of PCT/EP03/11814, filed on 12 September 2003 and incorporated herein by reference.

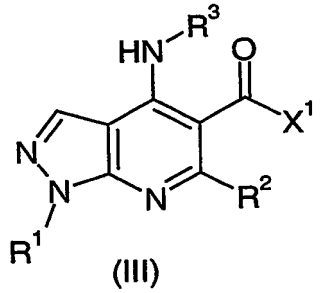
The present invention therefore also provides a method of preparing a compound of formula (I) or a salt thereof:



(I)

wherein R^1, R^2, R^3, R^4, R^5 and Ar are as defined, the method comprising :

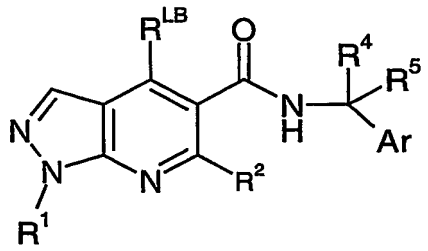
(a) reaction of an activated compound of formula (III),



(III)

wherein X^1 is a leaving group substitutable by an amine, with an amine of formula $ArCR^4R^5NH_2$;

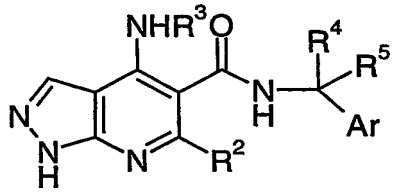
(b) reaction of a compound of formula (VII):



(VII)

, wherein R^{LB} is a leaving group which is displaceable by the amine of formula R^3NH_2, with an amine of formula R^3NH_2;

(c) reaction of a compound of formula (IXa) with an alkylating agent of formula R^1-X^3, where X^3 is a leaving group displaceable by the 1-position pyrazolopyridine nitrogen atom of the compound of formula (IXa):



(IXa)

;

or

(d) conversion of one compound of formula (I) or salt thereof into another compound of formula (I) or salt thereof;

and optionally converting the compound of formula (I) into a salt thereof e.g. a pharmaceutically acceptable salt thereof.

Preferred features of methods (a), (b), (c) and (d), independently of each other, are as described above for Processes A, B, C, and D, with all necessary changes being made.

The present invention also provides: (e) a method of preparing a pharmaceutically acceptable salt of a compound of formula (I) comprising conversion of the compound of formula (I) or a salt thereof into the desired pharmaceutically acceptable salt thereof. (See for example Example 307).

The present invention also provides a compound of formula (I) or a salt thereof, prepared by a method as defined herein.

Medical uses

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the diseases / conditions described herein (e.g. for use in the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal) and/or for use as a phosphodiesterase inhibitor e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of any of the diseases / conditions described herein in a mammal such as a human, e.g. for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of any of the diseases / conditions described herein in a mammal (e.g. human) in need thereof, e.g. a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which method comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are thought to be useful in the treatment and/or prophylaxis of a variety of diseases / conditions, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic obstructive pulmonary disease (COPD) (e.g. chronic bronchitis and/or emphysema), atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, multiple sclerosis, cognitive impairment (e.g. in a neurological disorder such as Alzheimer's disease), depression, or pain. Ulcerative colitis and/or Crohn's disease are collectively often referred to as inflammatory bowel disease.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD or asthma in a mammal (e.g. human).

PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, 59(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and references cited in the aforementioned publications).

PDE4 inhibitors are thought to be effective in the treatment of COPD. For example, see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and references cited in the aforementioned publications; and G. Krishna et al., *Expert Opinion on Investigational Drugs*, 2004, 13(3), 255-267 (see especially pp. 259-261 and refs. 102-111 and 201 therein). COPD is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (e.g., see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319).

PDE4 inhibitors are thought to be effective in the treatment of allergic rhinitis (e.g. see B.M. Schmidt et al., *J. Allergy & Clinical Immunology*, 108(4), 2001, 530-536).

PDE4 inhibitors are thought to be effective in the treatment of rheumatoid arthritis and multiple sclerosis (e.g. see H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; and A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and references cited in these publications). See e.g. A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473 and references cited therein for atopic dermatitis use.

PDE4 inhibitors have been suggested as having analgesic properties and thus being effective in the treatment of pain (A.Kumar et al., *Indian J. Exp. Biol.*, 2000, 38(1), 26-30).

In the invention, the treatment and/or prophylaxis can be of cognitive impairment e.g. cognitive impairment in a neurological disorder such as Alzheimer's disease. For example, the treatment and/or prophylaxis can comprise cognitive enhancement e.g. in a neurological disorder. See for example: H.T.Zhang et al. in: *Psychopharmacology*, June 2000, 150(3), 311-316 and *Neuropsychopharmacology*, 2000, 23(2), 198-204; and T. Egawa et al., *Japanese J. Pharmacol.*, 1997, 75(3), 275-81.

PDE4 inhibitors such as rolipram have been suggested as having antidepressant properties (e.g. J. Zhu et al., *CNS Drug Reviews*, 2001, 7(4), 387-398; O'Donnell, *Expert Opinion on Investigational Drugs*, 2000, 9(3), 621-625; and H.T. Zhang et al., *Neuropsychopharmacology*, October 2002, 27(4), 587-595).

Pharmaceutical compositions and dosing

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The invention also provides a method of preparing a pharmaceutical composition comprising a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers and/or excipients,

the method comprising mixing the compound or salt with the one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides a pharmaceutical composition prepared by said method.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. Accordingly , the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. More preferably, the pharmaceutical composition is suitable for inhaled or oral administration, e.g. to a mammal such as a human. Inhaled administration involves topical administration to the lung e.g. by aerosol or dry powder composition. Oral administration to a human is most preferred.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a syrup, suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. The carrier can for example be or include lactose, cellulose (for example microcrystalline cellulose), or mannitol. The tablet can also or instead

contain one or more pharmaceutically acceptable excipients, for example a binding agent such as hydroxypropylmethylcellulose or povidone (polyvinylpyrollidone), a lubricant e.g. an alkaline earth metal stearate such as magnesium stearate, and/or a tablet disintegrant such as sodium starch glycollate, croscarmellose sodium, or crospovidone (cross-linked polyvinylpyrollidone). The pharmaceutical composition being a tablet can be prepared by a method comprising the steps of: (i) mixing the compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, with the one or more pharmaceutically acceptable carriers and/or excipients, (ii) compressing the resulting mixture (which is usually in powder form) into tablets, and (iii) optionally coating the tablet with a tablet film-coating material.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets or powder containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous gum or an oil and the dispersion or suspension then filled into a soft gelatin capsule.

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, drops, gels or dry powders.

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide, or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

Particle size reduction of compound of formula (I) or salt thereof

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. Micronisation usually involves subjecting the compound/salt to collisional and/or abrasional forces in a fast-flowing circular or spiral/vortex-shaped airstream often including a cyclone component. The preferable particle size of the size-reduced (e.g. micronised) compound or salt is defined by a D50 value of about 0.5 to about 10 microns, e.g. about 1 to about 7 microns (e.g. as measured using laser diffraction). For example, it is preferable for the compound or salt of formula (I) to have a particle size defined by: a D10 of about 0.3 to about 3 microns (e.g. about 0.5 to about 2 microns, or about 1 micron), and/or a D50 of about 0.5 to about 10 microns or about 1 to about 7 microns (e.g. about 2 to about 5 microns or about 2 to about 4 microns), and/or a D90 of about 1 to about 30 microns or about 2 to about 20 microns or about 3 to about 15 microns (e.g. about 5 to about 15 microns or about 5 to about 10 microns); for example as measured using laser diffraction.

In particle size measurements, D90, D50 and D10 respectively mean that 90%, 50% and 10% of the material is less than the micron size specified. D50 is the median particle size. DV90, DV50 and DV10 respectively mean that 90%, 50% and 10% by volume of the material is less than the micron size specified. DM90, DM50 and DM10 respectively mean that 90%, 50% and 10% by weight of the material is less than the micron size specified.

Laser diffraction measurement of particle size can use a dry method (wherein a suspension of the compound/salt in an airflow crosses the laser beam) or a wet method [wherein a suspension of the compound/salt in a liquid dispersing medium, such as isooctane or (e.g. if compound is soluble in isooctane) 0.1% Tween 80 in water, crosses the laser beam]. With laser diffraction, particle size is preferably calculated using the Fraunhofer calculation; and/or preferably a Malvern Mastersizer or Sympatec apparatus is used for measurement. For example, particle size measurement and/or analysis by laser diffraction can use any or all of (preferably all of) the following: a Malvern Mastersizer longbed version, a dispersing medium of 0.1% Tween 80 in water, a stir rate of ca. 1500 rpm, ca. 3 mins sonification prior to final dispersion and analysis, a 300 RF (Reverse Fourier) lens, and/or the Fraunhofer calculation with Malvern software.

An illustrative non-limiting example of a small-scale micronisation process is now given:

Micronisation Example: Micronisation of Example 73, 98, 283, 304, 306 or 307

- Purpose: To micronize Example 73, 98, 283, 304, 306 or 307 (described hereinafter), usually in an amount of approximately 600-1000 mg thereof, using a Jetpharma MC1 micronizer.
- The parent (unmicronised) and micronised materials are analyzed for particle size by laser diffraction and crystallinity by PXRD.

Equipment and material

Equipment/material	Description and specification
Jetpharma MC1 Micronizer	Nitrogen supply: Air tank with 275psi rate tubing
Analytical balance	Sartorius Analytical
Top loader balance	Mettler PM400
Digital Caliper	VWR Electronic caliper
Vibrational spatula	Auto-spat Dispenser
Materials to be micronised	Example 73, 98, 283, 304, 306 or 307

The Jetpharma MC1 Micronizer comprises a horizontal disc-shaped milling housing having: a tubular compound inlet (e.g. angled at ca. 30 degrees to the horizontal) for entry of a suspension of unmicronised compound of formula (I) or salt in a gasflow, a separate gas inlet for entry of gases, a gas outlet for exit of gases, and a collection vessel for collecting micronised material. The milling housing has two chambers: (a) an outer annular chamber in gaseous connection with the gas inlet, the chamber being for receiving pressurised gas (e.g. air or nitrogen), and (b) a disc-shaped inner milling chamber within and coaxial with the outer chamber for micronising the input compound / salt, the two chambers being separated by an annular wall. The annular wall (ring R) has a plurality of narrow-bored holes connecting the inner and outer chambers and circumferentially-spaced-apart around the annular wall. The holes opening into the inner chamber are directed at an angle (directed part-way between radially and tangentially), and in use act as nozzles directing pressurised gas at high velocity from the outer chamber into the inner chamber and in an inwardly-spiral path (vortex) around the inner chamber (cyclone). The compound inlet is in gaseous communication with the inner chamber via a nozzle directed tangentially to the inner chamber, within and near to the annular wall / ring R. Upper and lower broad-diameter exit vents in the central axis of the inner milling chamber connect to (a) (lower exit) the collection vessel which has no air outlet, and (b) (upper exit) the gas outlet which leads to a collection bag, filter and a gas exhaust. Inside and coaxial with the tubular compound inlet and longitudinally-movable within it is positioned a venturi inlet (V) for entry of gases. The compound inlet also has a bifurcation connecting to an upwardly-directed material inlet port for inputting material.

In use, the narrow head of the venturi inlet (V) is preferably positioned below and slightly forward of the material inlet port so that when the venturi delivers pressurised gas (e.g. air or nitrogen) the feed material is sucked from the material inlet port into the gasstream thorough the compound inlet and is accelerated into the inner milling chamber

tangentially at a subsonic speed. Inside the milling chamber the material is further accelerated to a supersonic speed by the hole/nozzle system around the ring (R) (annular wall) of the milling chamber. The nozzles are slightly angled so that the acceleration pattern of the material is in the form of an inwardly-directed vortex or cyclone. The material inside the milling chamber circulates rapidly and particle collisions occur during the process, causing larger particles to fracture into smaller ones. "Centrifugal" acceleration in the vortex causes the larger particles to remain at the periphery of the inner chamber while progressively smaller particles move closer to the center until they exit the milling chamber, generally through the lower exit, at low pressure and low velocity. The particles that exit the milling chamber are heavier than air and settle downward thorugh the lower exit into the collection vessel, while the exhaust gas rises (together with a minority of small particles of micronised material) and escapes into the atmosphere at low pressure and low velocity.

Procedure:

The micronizer is assembled. The venturi protrusion distance from input port is preferably adjusted to about 1.0 cm respectively (e.g. so that the narrow head of the venturi inlet is positioned below and slightly forward of the material inlet port) and is measured with a micro-caliper to make sure that it is inserted correctly. The ring (R) and venturi (V) pressures are adjusted according to the values specified in the experimental design (refer to experimental section below) by adjusting the valves on the pressure gauges on the micronizer. The setup is checked for leakage by observing if there is any fluctuation in the reading of the pressure gauges.

Note that the venturi (V) pressure is kept at least 2 bars greater than the ring (R) pressure to prevent regurgitation of material, e.g. outwardly from the material inlet port.

Balance performance is checked with calibration weights. Specified amount of the parent material (see section on experimental run) is weighed into a plastic weigh boat. The material is then fed into the micronizer using a vibrational spatula (e.g. V-shaped in cross-section) at a specified feed rate. The material feeding time and equipment pressures are monitored during the micronization process.

Upon completion of the micronising run, the nitrogen supply is shut off and the collection bag is tapped to allow particles to settle into the recovery / collection vessel at the bottom of the micronizer. The collection bag is removed and set aside. The micronised powder in the recovery vessel (collection vessel) and the cyclone (above the recovery vessel) are collected separately into different weighed+labelled collection vials. The weight of the micronised material is recorded. The micronizer is disassembled and residual PDE4 compound on the micronizer inner surface is rinsed with 70/30 isopropyl alcohol / water and collected into a flask. The micronizer is then thoroughly cleaned by rinsing and wiping with suitable solvent and dried before subsequent runs are performed.

Preferred or Optional Experimental Parameters

Parent (unmicronised) material (Procedure 1): Example 73, 98, 283, 304, 306 or 307

Balance(s) Used: Sartorius analytical

Procedure no.	Material input amount (g)	Venturi Pressure (V) / ring (R) Pressure (bar)	Intended feed-rate	Time needed to feed material (min+sec)	Actual feed-rate (g/min)
1	ca. 0.9 g	V= 8 to 10 bar R= 5.5 to 6 bar	180 to 200 mg/min		procedure not carried out

The above optional parameters can be varied using the skilled person's knowledge.

Results and/or observations
% yield = [(Material from vessel + Material from cyclone)/Material input amount] x100
In general, very approximately 50-75% yields are achievable using this method, including material from collection vessel and material from inside walls of cyclone.

Procedure 1 includes possible parameters and conditions and has not been carried out.

Alternative embodiment: Any of the Examples of the compounds or salts of the invention disclosed herein can be micronised as described above.

Dry powder inhalable compositions

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose or starch, the compound of formula (I) or salt thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine, mannitol, trehalose and/or magnesium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by

volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 JD Zwolle, Netherlands).

In the dry powder inhalable composition, preferably, the compound of formula (I) or salt thereof is present in about 0.1% to about 70% (e.g. about 1% to about 50%, e.g. about 5% to about 40%, e.g. about 20 to about 30%) by weight of the composition.

An illustrative non-limiting example of a dry powder inhalable composition follows:

Dry Powder Formulation Example - Dry powder Lactose Blend Preparation

Using a size-reduced e.g. micronised form of the compound of formula (I) or salt thereof (e.g. as prepared in the Micronisation Example above), the dry powder blend is prepared by mixing the required amount of the compound/salt (e.g. 10 mg, 1% w/w) with inhalation-grade lactose containing 10% fines (e.g. 990 mg, 99% w/w) in a Teflon™ (polytetrafluoroethene) pot in a Mikro-dismembrator ball-mill (but without a ball bearing) at ¾ speed (ca. 2000-2500 rpm) for about 4 hours at each blend concentration. The Mikro-dismembrator (available from B. Braun Biotech International, Schwarzenberger Weg 73-79, D-34212 Melsungen, Germany; www.bbraunbiotech.com) comprises a base with an upwardly-projecting and sidewardly-vibratable arm to which is attached the Teflon ™ pot. The vibration of the arm achieves blending.

Other blends: 10% w/w compound/salt (50 mg) + 90% w/w lactose (450 mg, inhalation-grade lactose containing 10% fines).

Serial dilution of the 1% w/w blend can achieve e.g. 0.1% and 0.3% w/w blends.

Dry powder inhalation devices

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose, e.g. of the dry powder composition, can be administered by inhalation via a device such as the DISKUS ™ device, marketed by GlaxoSmithKline. The DISKUS ™ inhalation device is usually substantially as described in GB 2,242,134 A. In such device at least one container for the pharmaceutical composition in powder form (the at least one container preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: means defining an opening station for the said at least one container; means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

Unit dose form and dosing regimens

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

In the pharmaceutical composition, a or each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. A or each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

A pharmaceutically acceptable compound or salt of the invention is preferably administered to a mammal (e.g. human) in a daily oral or parenteral dose of 0.001 mg to 50 mg per kg body weight per day (mg/kg/day), for example 0.01 to 20 mg/kg/day or 0.03 to 10 mg/kg/day or 0.1 to 2 mg/kg/day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

A pharmaceutically acceptable compound or salt of the invention is preferably administered to a mammal (e.g. human) in a daily nasal or inhaled dose of: 0.0001 to 5 mg/kg/day or 0.0001 to 1 mg/kg/day, e.g. 0.001 to 1 mg/kg/day or 0.001 to 0.3 mg/kg/day or 0.001 to 0.1 mg/kg/day or 0.005 to 0.3 mg/kg/day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention is preferably administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day e.g. 2 to 500 mg per day, or a nasal or inhaled dose of 0.001 to 300 mg per day or 0.001 to 50 mg per day or 0.01 to 30 mg per day or 0.01 to 5 mg per day or 0.02 to 2 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

Combinations

The compounds, salts and/or pharmaceutical compositions according to the invention may also be used in combination with another therapeutically active agent, for example, a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic or an anti-inflammatory agent.

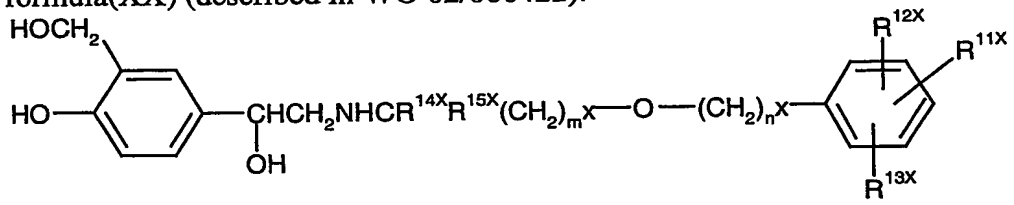
The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another therapeutically active agent, for example, a β_2-adrenoreceptor agonist, an anti-histamine, an anti-allergic, an anti-inflammatory agent or an antiinfective agent.

Preferably, the β_2-adrenoreceptor agonist is salmeterol (e.g. as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline, or a salt thereof (e.g. pharmaceutically acceptable salt thereof), for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the

fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 12-24 hour period such as salmeterol or formoterol. Preferably, the β_2-adrenoreceptor agonist is for inhaled administration, e.g. once per day and/or for simultaneous inhaled administration; and more preferably the β_2-adrenoreceptor agonist is in particle-size-reduced form e.g. as defined herein. Preferably, the β_2-adrenoreceptor agonist combination is for treatment and/or prophylaxis of COPD or asthma. Salmeterol or a pharmaceutically acceptable salt thereof, e.g. salmeterol xinofoate, is preferably administered to humans at an inhaled dose of 25 to 50 micrograms twice per day (measured as the free base). The combination with a β_2-adrenoreceptor agonist can be as described in WO 00/12078.

Preferred long acting β_2-adrenoreceptor agonists include those described in WO 02/066422A, WO 03/024439, WO 02/070490 and WO 02/076933.

Especially preferred long-acting β_2-adrenoreceptor agonists include compounds of formula(XX) (described in WO 02/066422):



(XX)

or a salt or solvate thereof, wherein in formula (XX):

m^X is an integer of from 2 to 8;

n^X is an integer of from 3 to 11,

with the proviso that $m^X + n^X$ is 5 to 19,

R^{11X} is $-XSO_2NR^{16X}R^{17X}$ wherein X is $-(CH_2)_{p^X}-$ or C_{2-6} alkenylene;

R^{16X} and R^{17X} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^{18X}R^{19X}$, phenyl, and phenyl (C_{1-4}alkyl)-,

or R^{16X} and R^{17X}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R^{16X} and R^{17X} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^{18X}$, $-SO_2NR^{18X}R^{19X}$, $-CONR^{18X}R^{19X}$, $-NR^{18X}C(O)R^{19X}$, or a 5-, 6- or 7-membered heterocylic ring;

R^{18X} and R^{19X} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and

p^X is an integer of from 0 to 6, preferably from 0 to 4;

R^{12X} and R^{13X} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and

R^{14X} and R^{15X} are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^{14X} and R^{15X} is not more than 4.

Preferred β_2-adrenoreceptor agonists disclosed in WO 02/066422 include: 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl}amino)hexyl]oxy}butyl)benzenesulfonamide and 3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide.

A preferred β_2-adrenoreceptor agonist disclosed in WO 03/024439 is: 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol..

A combination of a compound of formula (I) or salt together with an anti-histamine is preferably for oral administration (e.g. as a combined composition such as a combined tablet), and can be for treatment and/or prophylaxis of allergic rhinitis. Examples of anti-histamines include methapyrilene, or H1 antagonists such as cetirizine, loratadine (e.g. Clarityn ^{TM}), desloratadine (e.g. Clarinex ^{TM}) or fexofenadine (e.g. Allegra ^{TM}).

The invention also provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic compound, e.g. a muscarinic (M) receptor antagonist in particular an M_1, M_2, M_1/M_2, or M_3 receptor antagonist, more preferably a M_3 receptor antagonist, still more preferably a M_3 receptor antagonist which selectively antagonises (e.g. antagonises 10 times or more strongly) the M_3 receptor over the M_1 and/or M_2 receptor. For combinations of anticholinergic compounds / muscarinic (M) receptor antagonist with PDE4 inhibitors, see for example WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312 A1, and some or all of these publications give examples of anticholinergic compounds / muscarinic (M) receptor antagonists which may be used with the compounds of formula (I) or salts, and/or suitable pharmaceutical compositions. For example, the muscarinic receptor antagonist can comprise or be an ipratropium salt (e.g. ipratropium bromide), an oxitropium salt (e.g. oxitropium bromide), or more preferably a tiotropium salt (e.g. tiotropium bromide); see e.g. EP 418 716 A1 for tiotropium.

The anticholinergic compound or muscarinic (M) receptor antagonist, e.g. M_3 receptor antagonist, is preferably for inhaled administration, more preferably in particle-size-reduced form e.g. as defined herein. More preferably, both the muscarinic (M) receptor antagonist and the compound of formula (I) or the pharmaceutically acceptable salt thereof are for inhaled administration. Preferably, the anticholinergic compound or muscarinic receptor antagonist and the compound of formula (I) or salt are for simultaneous administration. The muscarinic receptor antagonist combination is preferably for treatment and/or prophylaxis of COPD.

Other suitable combinations include, for example, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another anti-inflammatory agent such as an anti-inflammatory corticosteroid; or a non-steroidal anti-inflammatory drug (NSAID) such as a leukotriene antagonist (e.g. montelukast), an iNOS inhibitor, a tryptase inhibitor, a elastase inhibitor, a beta-2 integrin antagonist, a adenosine 2a agonist, a CCR3 antagonist, or a 5-lipoxogenase inhibitor; or an antiinfective agent (e.g. an antibiotic or an antiviral). An iNOS inhibitor is preferably for oral administration. Suitable iNOS inhibitors (inducible nitric oxide synthase inhibitors) include those disclosed in WO 93/13055, WO 98/30537, WO 02/50021, WO 95/34534 and WO 99/62875. Suitable CCR3 inhibitors include those disclosed in WO 02/26722.

In a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anti-inflammatory corticosteroid (which is preferably for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis), then preferably the anti-inflammatory corticosteroid is fluticasone, fluticasone propionate (e.g. see US patent 4,335,121), beclomethasone, beclomethasone 17-propionate ester, beclomethasone 17,21-dipropionate ester, dexamethasone or an ester thereof, mometasone or an ester thereof, ciclesonide, budesonide, flunisolide, or a compound as described in WO 02/12266 A1 (e.g. as claimed in any of claims 1 to 22 therein), or a pharmaceutically acceptable salt of any of the above. If the anti-inflammatory corticosteroid is a compound as described in WO 02/12266 A1, then preferably it is Example 1 therein {which is 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester} or Example 41 therein {which is 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester}, or a pharmaceutically acceptable salt thereof. The anti-inflammatory corticosteroid is preferably for intranasal or inhaled administration. Fluticasone propionate is preferred and is preferably for inhaled administration to a human either (a) at a dose of 250 micrograms once per day or (b) at a dose of 50 to 250 micrograms twice per day.

Also provided is a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with β_2-adrenoreceptor agonist and an anti-inflammatory corticosteroid, for example as described in WO 03/030939 A1. Preferably this combination is for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis. The β_2-adrenoreceptor agonist and/or the anti-inflammatory corticosteroid can be as described above and/or as described in WO 03/030939 A1. Most preferably, in this "triple" combination, the β_2-adrenoreceptor agonist is salmeterol or a pharmaceutically acceptable salt thereof (e.g. salmeterol xinafoate) and the anti-inflammatory corticosteroid is fluticasone propionate.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical composition.

In one embodiment, the combination as defined herein can be for simultaneous inhaled administration and is disposed in a combination inhalation device. Such a combination inhalation device is another aspect of the invention. Such a combination inhalation device can comprise a combined pharmaceutical composition for simultaneous inhaled administration (e.g. dry powder composition), the composition comprising all the individual compounds of the combination, and the composition being incorporated into a plurality of sealed dose containers mounted longitudinally in a strip or ribbon inside the inhalation device, the containers being rupturable or peel-openable on demand; for example such inhalation device can be substantially as described in GB 2,242,134 A (DISKUS ^{TM}) and/or as described above. Alternatively, the combination inhalation device can be such that the individual compounds of the combination are administrable simultaneously but are stored separately (or wholly or partly stored separately for triple combinations), e.g. in separate pharmaceutical compositions, for example as described in PCT/EP03/00598 filed on 22 January 2003, published as WO 03/061743 (e.g. as described in the claims thereof e.g. claim 1).

The invention also provides a method of preparing a combination as defined herein, the method comprising either

(a) preparing a separate pharmaceutical composition for administration of the individual compounds of the combination either sequentially or simultaneously, or

(b) preparing a combined pharmaceutical composition for administration of the individual compounds of the combination simultaneously,

wherein the pharmaceutical composition comprises the combination together with one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides a combination as defined herein, prepared by a method as defined herein.

BIOLOGICAL TEST METHODS

PDE 3, PDE 4B, PDE 4D, PDE 5, PDE 6 Primary assay methods

The activity of the compounds can be measured in the assay methods shown below. Preferred compounds of the invention are selective PDE4 inhibitors, i.e. they inhibit PDE4 (e.g. PDE4B and/or PDE4D, preferably PDE4B) more strongly than they inhibit PDE3 and/or more strongly than they inhibit PDE5 and/or more strongly than they inhibit PDE6.

PDE enzyme sources and literature references

Human recombinant PDE4B, in particular the 2B splice variant thereof (HSPDE4B2B), is disclosed in WO 94/20079 and also M.M. McLaughlin et al., "A low *K*m, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA", *J. Biol. Chem.*, 1993, **268**, 6470-6476. For example, in Example 1 of WO 94/20079, human recombinant PDE4B is described as being expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62, e.g. after induction by addition of 150 uM $CuSO_4$, and 100,000 x *g* supernatant fractions of yeast cell lysates are described for use in the harvesting of PDE4B enzyme.

Human recombinant PDE4D (HSPDE4D3A) is disclosed in P. A. Baecker et al., "Isolation of a cDNA encoding a human rolipram-sensitive cyclic AMP phoshodiesterase (PDE IV_D)", *Gene*, 1994, **138**, 253-256.

Human recombinant PDE5 is disclosed in K. Loughney et al., "Isolation and characterisation of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3',5'-cyclic nucleotide phosphodiesterase", *Gene*, 1998, **216**, 139-147.

PDE3 was purified from bovine aorta as described by H. Coste and P. Grondin, "Characterisation of a novel potent and specific inhibitor of type V phosphodiesterase", *Biochem. Pharmacol.*, 1995, **50**, 1577-1585.

PDE6 was purified from bovine retina as described by: P. Catty and P. Deterre, "Activation and solubilization of the retinal cGMP-specific phosphodiesterase by limited proteolysis", *Eur. J. Biochem.*, 1991, **199**, 263-269; A. Tar et al. "Purification of bovine retinal cGMP phosphodiesterase", *Methods in Enzymology*, 1994, **238**, 3-12; and/or D. Srivastava et al. "Effects of magnesium on cyclic GMP hydrolysis by the bovine retinal rod cyclic GMP phosphodiesterase", *Biochem. J.*, 1995, **308**, 653-658.

Inhibition of PDE 3, PDE 4B, PDE 4D, PDE 5 or PDE 6 activity: radioactive Scintillation Proximity Assay (SPA)

The ability of compounds to inhibit catalytic activity at PDE4B or 4D (human recombinant), PDE3 (from bovine aorta), PDE5 (human recombinant) or PDE6 (from bovine retina) is determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds (as a solution in DMSO, preferably about 2 microlitre (ul) volume of DMSO solution) are preincubated at ambient temperature (room temperature, e.g. 19-23°C) in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5 , 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes (usually 30 minutes). The enzyme concentration is adjusted so that no more than 20% hydrolysis of the substrate defined below occurred in control wells without compound, during the incubation. For the PDE3, PDE4B and PDE4D assays, [5',8-^{3}H]Adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK.559; or Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8 4SP, UK) is added to give 0.05uCi per well and ~ 10nM final concentration. For the PDE5 and PDE6 assays, [8-^{3}H]Guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK.392) is added to give 0.05uCi per well and ~ 36nM final concentration. Plates containing assay mixture, preferably approx. 100 ul volume of assay mixture, are mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) are added (~1mg per well) to terminate the assay. Plates are sealed and shaken and allowed to stand at ambient temperature for 35 minutes to 1hour (preferably 35 minutes) to allow the beads to settle. Bound radioactive product is measured using a WALLAC TRILUX 1450 Microbeta scintillation counter. For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound are assayed. Curves are analysed using ActivityBase and XLfit (ID Business Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kingdom) Results are expressed as pIC_{50} values.

In an alternative to the above radioactive SPA assay, PDE4B or PDE4D inhibition can be measured in the following Fluorescence Polarisation (FP) assay:

Inhibition of PDE4B or PDE4D activity: Fluorescence Polarisation (FP) assay

The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant) or PDE4D (human recombinant) is determined by IMAP Fluorescence Polarisation (FP) assay (IMAP Explorer kit, available from Molecular Devices Corporation, Sunnydale, CA, USA; Molecular Devices code: R8062) in 384-well format. The IMAP FP assay is able to measure PDE activity in an homogenous, non-radioactive assay format. The FP assay uses the ability of immobilised trivalent metal cations, coated onto nanoparticles (tiny beads), to bind the phosphate group of Fl-AMP that is produced on the hydrolysis of fluorescein-labelled (Fl) cyclic adenosine mono-phosphate (Fl-cAMP) to the non-cyclic Fl-AMP form. Fl-cAMP does not bind. Binding of Fl-AMP product to the beads (coated with the immobilised trivalent cations) slows the rotation of

the bound Fl-AMP and leads to an increase in the fluorescence polarisation ratio of parallel to perpendicular light. Inhibition of the PDE reduces/inhibits this signal increase.

Test compounds (small volume, e.g. ca. 0.5 to 1 ul, preferably ca. 0.5 ul, of solution in DMSO) are preincubated at ambient temperature (room temperature, e.g. 19-23°C) in black 384-well microtitre plates (supplier: NUNC, code 262260) with PDE enzyme in 10mM Tris-HCl buffer pH 7.2, 10mM $MgCl_2$, 0.1% (w/v) bovine serum albumin, and 0.05% NaN_3 for 10-30 minutes. The enzyme level is set by experimentation so that reaction was linear throughout the incubation. Fluorescein adenosine 3',5'-cyclic phosphate (from Molecular Devices Corporation, Molecular Devices code: R7091) is added to give about 40nM final concentration (final assay volume usually ca. 20-40 ul, preferably ca. 20 ul). Plates are mixed on an orbital shaker for 10 seconds and incubated at ambient temperature for 40 minutes. IMAP binding reagent (as described above, from Molecular Devices Corporation, Molecular Devices code: R7207) is added (60ul of a 1 in 400 dilution in binding buffer of the kit stock solution) to terminate the assay. Plates are allowed to stand at ambient temperature for 1 hour. The Fluorescence Polarisation (FP) ratio of parallel to perpendicular light is measured using an Analyst^{TM} plate reader (from Molecular Devices Corporation). For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound are assayed. Curves are analysed using ActivityBase and XLfit (ID Business Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kingdom). Results are expressed as pIC_{50} values.

In the FP assay, all reagents are dispensed using Multidrop^{TM} (available from Thermo Labsystems Oy, Ratastie 2, PO Box 100, Vantaa 01620, Finland).

For a given PDE4 inhibitor, the PDE4B (or PDE4D) inhibition values measured using the SPA and FP assays can differ slightly. However, in a regression analysis of 100 test compounds (not necessarily compounds of the invention), the pIC_{50} inhibition values measured using SPA and FP assays have been found generally to agree within 0.5 log units, for PDE4B and PDE4D (linear regression coefficient 0.966 for PDE4B and 0.971 for PDE4D; David R.Mobbs et al., "Comparison of the IMAP Fluorescence Polarisation Assay with the Scintillation Proximity Assay for Phosphodiesterase Activity", poster presented at 2003 Molecular Devices UK & Europe User Meeting, 2nd October 2003, Down Hall, Harlow, Essex, United Kingdom).

Biological Data obtained for some of the Examples (PDE4B inhibitory activity, either as one reading or as an average of ca. 2-6 readings) are as follows, based on current measurements only. In each of the SPA and FP assays, absolute accuracy of measurement is not possible, and the readings given are accurate only up to about ± 0.5 of a log unit, depending on the number of readings made and averaged:

Example number	**PDE4B pIC_{50}** (± about 0.5)
1, 8, 24, 28	8.3 to 8.8
6, 7, 26, 29	7.15 to 7.45

10, 13	8.3 to 8.5
48, 73, 98, 139, 210, 218, 221, 252, 261, 282	8.7 to 10.0
Examples 308 to 314	8.0 to 9.45

A large majority or substantially all of the Examples have been tested for PDE4B inhibition using the radioactive SPA assay or the FP assay. A large majority or substantially all of the Examples tested have PDE4B inhibitory activities in the range of pIC_{50} = about 6 (± about 0.5) to about 10 (± about 0.5).

The Examples wherein R^3 = cyclohexyl (NHR^3 = sub-formula (c)), tetrahydro-2H-pyran-4-yl (NHR^3 = group (h)), 4-oxocyclohexyl (NHR^3 = sub-formula (o)), or certain other types of substituted cyclohexyl or certain heterocycles, usually or often (especially with R^1 = ethyl) have a higher level of selectivity for PDE4B over PDE5, as measured in the above enzyme inhibition assays, compared to the selectivities of comparable Examples wherein R^3 = cyclopropyl (NHR^3 = sub-formula (b)). For example, based on current measurements only, and subject to cumulative assay inaccuracies:
- Examples 21, 40, 90, 198 and 201 (wherein NHR^3 = sub-formula (h), (c), (j), (n) and (o) respectively, R^1 = ethyl) have selectivities for PDE4B over PDE5 in the range of about 3 to 20 or more times greater than the selectivity achieved for the equivalent Example 39 wherein R^3 = cyclopropyl (NHR^3 = sub-formula (b));
- Examples 43 and 44 (wherein NHR^3 = sub-formula (c) and (h) respectively) have selectivities for PDE4B over PDE5 in the range of about 4 to 8 or more times greater than the selectivity achieved for the equivalent R^3 = cyclopropyl Example 42;
- Examples 22 and 48 (wherein NHR^3 = sub-formula (h) and (c) respectively) have selectivities for PDE4B over PDE5 in the range of about 2.5 to 10 or more times greater than the selectivity achieved for the equivalent R^3 = cyclopropyl Example 47; and
- Examples 2 and 3 (wherein NHR^3 = sub-formula (c) and (h) respectively) have selectivities for PDE4B over PDE5 in the range of about 2 to 5 or more times greater than the selectivity achieved for the equivalent R^3 = cyclopropyl Example 1.

Emesis: Some known PDE4 inhibitors can cause emesis and/or nausea to greater or lesser extents (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable, but not essential, if a PDE4 inhibitory compound or salt of the invention were to cause only limited or manageable emetic side-effects. Emetic side-effects can for example be measured by the emetogenic potential of the compound or salt when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting, retching and/or writhing in ferrets after oral or parenteral administration of the compound or salt. See for example In vivo Assay 4 hereinafter for a measurement method for anti-inflammatory effect, emetic side-effects and therapeutic

index (TI) in the ferret. See also for example A. Robichaud et al., "Emesis induced by inhibitors of [PDE IV] in the ferret", *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465. However, optionally, emetic side-effects and therapeutic index (TI) in rats can be conveniently measured by monitoring the pica feeding behaviour of rats after administration of the compound or salt of the invention (see In Vivo Assay 2 below).

Other side effects: Some known PDE4 inhibitors can cause other side effects such as headache and other central nervous sytem (CNS-) mediated side effects; and/or gastrointestinal (GI) tract disturbances. Therefore, it would be preferable but not essential if a particular PDE4 inhibitory compound or salt of the invention were to cause only limited or manageable side-effects in one or more of these side-effect categories.

***In Vivo* Biological Assays**

The *in vitro* enzymatic PDE4B inhibition assay described above should be regarded as being the primary test of biological activity. However, additional *in vivo* biological tests, which are optional and which are not an essential measure of efficacy or side-effects, are described below.

In Vivo Assay 1. LPS-induced pulmonary neutrophilia in rats: effect of orally administered PDE4 inhibitors

Pulmonary neutrophil influx has been shown to be a significant component to the family of pulmonary diseases like chronic obstructive pulmonary disease (COPD) which can involve chronic bronchitis and/or emphysema (G.F. Filley, *Chest.* 2000; 117(5); 251s-260s). The purpose of this neutrophilia model is to study the potentially anti-inflammatory effects *in vivo* of orally administered PDE4 inhibitors on neutrophilia induced by inhalation of aerosolized lipopolysaccharide (LPS), modelling the neutrophil inflammatory component(s) of COPD. See the literature section below for scientific background.

Male Lewis rats (Charles River, Raleigh, NC, USA) weighing approximately 300-400 grams are pretreated with either (a) test compound suspended in 0.5% methylcellulose (obtainable from Sigma-Aldrich, St Louis, MO, USA) in water or (b) vehicle only, delivered orally in a dose volume of 10 ml/kg. Generally, dose response curves are generated using the following doses of PDE4 inhibitors: 10.0, 2.0, 0.4, 0.08 and 0.016 mg/kg. Thirty minutes following pretreatment, the rats are exposed to aerosolized LPS (Serotype E. Coli 026:B6 prepared by trichloroacetic acid extraction, obtainable from Sigma-Aldrich, St Louis, MO, USA), generated from a nebulizer containing a 100 μg/ml LPS solution. Rats are exposed to the LPS aerosol at a rate of 4 L/min for 20 minutes. LPS exposure is carried out in a closed chamber with internal dimensions of 45 cm length x 24 cm width x 20 cm height. The nebulizer and exposure chamber are contained in a certified fume hood. At 4 hours-post LPS exposure the rats are euthanized by overdose with pentobarbital at 90 mg/kg, administered intraperitoneally. Bronchoalveolar lavage (BAL) is performed through a 14 gauge blunt needle into the exposed trachea. Five, 5 ml washes are performed to collect a total of 25 ml of BAL fluid. Total cell counts and leukocyte differentials are performed on BAL fluid in order to calculate neutrophil influx into the lung. Percent neutrophil inhibition at each dose (cf. vehicle) is calculated and a variable slope, sigmoidal dose-response curve is generated, usually using Prism Graph-Pad. The dose-response curve is used to calculate an ED50 value (in mg per kg of body weight) for inhibition by the PDE4 inhibitor of the LPS-induced neutrophilia.

Alternative method : In an alternative embodiment of the procedure, a single oral dose of 10 mg/kg or 1.0 mg/kg of the PDE4 inhibitor (or vehicle) is administered to the rats, and percent neutrophil inhibition is calculated and reported for that specific dose.

Literature:

Filley G.F. Comparison of the structural and inflammatory features of COPD and asthma. *Chest.* 2000; 117(5) 251s-260s.

Howell RE, Jenkins LP, Fielding LE, and Grimes D. Inhibition of antigen-induced pulmonary eosinophilia and neutrophilia by selective inhibitors of phosphodiesterase types 3 and 4 in brown Norway rats. *Pulmonary Pharmacology.* 1995; 8: 83-89.

Spond J, Chapman R, Fine J, Jones H, Kreutner W, Kung TT, Minnicozzi M. Comparison of PDE 4 inhibitors, Rolipram and SB 207499 (Ariflo™), in a rat model of pulmonary neutrophilia. *Pulmonary Pharmacology and Therapeutics.* 2001; 14: 157-164.

Underwood DC, Osborn RR, Bochnowicz S, Webb EF, Rieman DJ, Lee JC, Romanic AM, Adams JL, Hay DWP, and Griswold DE. SB 239063, a p38 MAPK

inhibitor, reduces neutrophilia, inflammatory cytokines, MMP-9, and fibrosis in lung. *Am J Physiol Lung Cell Mol Physiol.* 2000; 279: L895-L902.

In Vivo Assay 2. ***Rat Pica Model of emesis***

Background: Selective PDE4 inhibitors have been shown to inhibit inflammation in various *in vitro* and *in vivo* models by increasing intracellular levels of cAMP of many immune cells (e.g. lymphocytes, monocytes). However, a side effect of some PDE4 inhibitors in many species is emesis. Because many rat models of inflammation are well characterized, they have been used in procedures (see e.g. In Vivo Assay 1 above) to show beneficial anti-inflammatory effects of PDE 4 inhibitors. However rats have no emetic response (they have no vomit reflex), so that the relationship between beneficial anti-inflammatory effects of PDE 4 inhibitors and emesis is difficult to study directly in rats.

However, in 1991, Takeda *et al.* (see Literature section below) demonstrated that the pica feeding response is analogous to emesis in rats. Pica feeding is a behavioural response to illness in rats wherein rats eat non-nutritive substances such as earth or in particular clay (e.g. kaolin) which may help to absorb toxins. Pica feeding can be induced by motion and chemicals (especially chemicals which are emetic in humans), and can be inhibited pharmacologically with drugs that inhibit emesis in humans. The Rat Pica Model, In Vivo Assay 2, can determine the level of pica response of rats to PDE 4 inhibition at pharmacologically relevant doses in parallel to *in vivo* anti-inflammatory Assays in (a separate set of) rats (e.g. In Vivo Assay 1 above).

Anti-inflammatory and pica assays in the same species together can provide data on the "therapeutic index" (TI) in the rat of the compounds/salts of the invention. The Rat TI can for example be calculated as the ratio of a) the potentially-emetic Pica Response ED50 dose from Assay 2 to b) the rat anti-inflammatory ED50 dose (e.g. measured by rat neutrophilia-inhibition in eg In Vivo Assay 1), with larger TI ratios possibly indicating lower emesis at many anti-inflammatory doses. This might allow a choice of a non-emetic or minimal-emetic pharmaceutical dose of the compounds or salts of the invention which has an anti-inflammatory effect. It is recognised however that achieving a low-emetic PDE4 inhibitory compound is not essential to the invention.

Procedure: On the first day of the experiment, the rats are housed individually in cages without bedding or "enrichment". The rats are kept off of the cage floor by a wire screen. Pre-weighed food cups containing standard rat chow and clay pellets are placed in the cage. The clay pellets, obtainable from Languna Clay Co, City of Industry, CA, USA, are the same size and shape as the food pellets. The rats are acclimated to the clay for 72 hours, during which time the cups and food and clay debris from the cage are weighed daily on an electronic balance capable of measuring to the nearest 0.1 grams. By the end of the 72 hour acclimation period the rats generally show no interest in the clay pellets.

At the end of 72 hours the rats are placed in clean cages and the food cups weighed. Rats that are still consuming clay regularly are removed from the study. Immediately prior to the dark cycle (the time when the animals are active and should be eating) the animals are split into treatment groups and dosed orally with a dose of the compound/salt of the invention (different doses for different treatment groups) or with vehicle alone, at a dose volume of 2 ml/kg. In this oral dosing, the compound/salt is in

the form of a suspension in 0.5% methylcellulose (obtainable Sigma-Aldrich, St. Louis, MO, USA) in water. The food and clay cups and cage debris are weighed the following day and the total clay and food consumed that night by each individual animal is calculated.

A dose response is calculated by first converting the data into quantal response, where animals are either positive or negative for the pica response. A rat is "pica positive" if it consumes greater than or equal to 0.3 grams of clay over the mean of is usually calculated using logistic regression performed by the Statistica software statistical package. A Pica Response ED50 value in mg per kg of body weight can then be calculated.

The Pica Response ED50 value can be compared to the neutrophilia-inhibition ED50 values for the same compound administered orally to the rat (measurable by In Vivo Assay 1 above), so that a Therapeutic Index (TI) in rats can be calculated thus:

$$\text{Rat Therapeutic index (TI) (50/50)} = \frac{\text{Pica Response ED50 value}}{\text{rat neutrophilia-inhibition ED50 value}}$$

In general, the Therapeutic Index (TI) calculated this way is often substantially different to, and for example can often be substantially higher than, the TI (D20/D50) calculated in the ferret (see In vivo Assay 4 below).

Literature:

Beavo JA, Contini, M., Heaslip, R.J. Multiple cyclic nucleotide phosphodiesterases. *Mol Pharmacol.* 1994; 46:399-405.

Spond J, Chapman R, Fine J, Jones H, Kreutner W, Kung TT, Minnicozzi M. Comparison of PDE 4 inhibitors, Rolipram and SB 207499 (Ariflo™), in a rat model of pulmonary neutrophilia. *Pulmonary Pharmacology and Therapeudtics.* 2001; 14:157-164.

Takeda N, Hasegawa S, Morita M, and Matsunaga T. Pica in rats is analogous to emesis: an animal model in emesis research. *Pharmacology, Biochemistry and Behavior.* 1991; 45:817-821.

Takeda N, Hasegawa S, Morita M, Horii A, Uno A, Yamatodani A and Matsunaga T. Neuropharmacological mechanisms of emesis. I . Effects of antiemetic drugs on motion- and apomorphine-induced pica in rats. *Meth Find Exp Clin Pharmacol.* 1995; 17(9) 589-596.

Takeda N, Hasegawa S, Morita M, Horii A, Uno A, Yamatodani A and Matsunaga T. Neuropharmacological mechanisms of emesis. II . Effects of antiemetic drugs on cisplatin-induced pica in rats. *Meth Find Exp Clin Pharmacol.* 1995; 17(9) 647-652.

In Vivo Assay 3. LPS induced pulmonary neutrophilia in rats: effect of intratracheally administered PDE4 inhibitors

This assay is an animal model of inflammation in the lung – specifically neutrophilia induced by lipopolysaccharide (LPS) – and allows the study of putative inhibition of such neutrophilia (anti-inflammatory effect) by intratracheally (i.t.) administered PDE4 inhibitors. The PDE4 inhibitors are preferably in dry powder or wet

suspension form. I.t. administration is one model of inhaled administration, allowing topical delivery to the lung.

Animals: Male CD (Sprague Dawley Derived) rats supplied by Charles River, Raleigh, NC, USA are housed in groups of 5 rats per cage, acclimatised after delivery for at least 7 days with bedding/nesting material regularly changed, fed on SDS diet R1 pelleted food given *ad lib,* and supplied with daily-changed pasteurised animal grade drinking water.

Device for dry powder administration: Disposable 3-way tap between dosing needle and syringe. A 3-way sterile tap (Vycon Ref 876.00) is weighed, the drug blend or inhalation grade lactose (vehicle control) is then added to the tap, the tap closed to prevent loss of drug, and the tap is re-weighed to determine the weight of drug in the tap. After dosing, the tap is weighed again to determine the weight of drug that had left the tap. The needle, a Sigma Z21934-7 syringe needle 19-gauge 152 mm (6 inches) long with luer hub, is cut by engineering to approximately 132 mm (5.2 inches), a blunt end is made to prevent them damaging the rat's trachea, and the needle is weighed prior to and after drug delivery to confirm that no drug was retained in the needles after dosing.

Device for wet suspension administration: This is the similar to the above but a blunt dosing needle, whose forward end was slightly angled to the needle axis, is used, with a flexible plastic portex canula inserted into the needle.

Drugs and Materials: Lipopolysaccharide (LPS) (Serotype:0127:B8) (L3129 Lot 61K4075) is dissolved in phosphate-buffered saline (PBS). PDE4 inhibitors are used in size-reduced (e.g. micronised) form, for example according to the Micronisation Example given above. For dry powder administration of the drug, the Dry Powder Formulation Example given above, comprising drug and inhalation-grade lactose, can be used. The inhalation-grade lactose usually used (Lot E98L4675 Batch 845120) has 10% fines (10% of material under 15um particle size measured by Malvern particle size).
Wet suspensions of the drug can be prepared by adding the required volume of vehicle to the drug; the vehicle used being a mixture of saline/tween (0.2% tween 80). The wet suspension is sonicated for 10 minutes prior to use.

Preparation, and dosing with PDE 4 inhibitor: Rats are anaesthetised by placing the animals in a sealed Perspex chamber and exposing them to a gaseous mixture of isoflourane (4.5 %), nitrous oxide (3 litres.minute^{-1}) and oxygen (1 litre.minute^{-1}). Once anaesthetised, the animals are placed onto a stainless steel i.t. dosing support table. They are positioned on their back at approximately a 35° angle. A light is angled against the outside of the throat to highlight the trachea. The mouth is opened and the opening of the upper airway visualised. The procedure varies for wet suspension and dry powder administration of PDE4 inhibitors as follows:

Dosing with a Wet suspension: A portex cannula is introduced via a blunt metal dosing needle that has been carefully inserted into the rat trachea. The animals are intratracheally dosed with vehicle or PDE4 inhibitor via the dosing needle with a new internal canula used for each different drug group. The formulation is slowly (10 seconds) dosed into the trachea using a syringe attached to the dosing needle.

Dosing with a Dry Powder: The three-way tap device and needle are inserted into the rat trachea up to a pre-determined point established to be located approximately 1 cm above the primary bifurcation. Another operator holds the needle at the specified position whilst 2x 4ml of air is delivered through the three-way tap by depressing the syringes (ideally coinciding with the animal inspiring), aiming to expel the entire drug quantity from the tap. After dosing, the needle and tap are removed from the airway and the tap closed off to prevent any retained drug leaving the tap.

After dosing with either wet suspension or dry powder, the animals are then removed from the table and observed constantly until they have recovered from the effects of anaesthesia. The animals are returned to the holding cages and given free access to food and water; they are observed and any unusual behavioural changes noted.

Exposure to LPS: About 2 hours after i.t. dosing with vehicle control or the PDE4 inhibitor, the rats are placed into sealed Perspex containers and exposed to an aerosol of LPS (nebuliser concentration 150 $\mu g.ml^{-1}$) for 15 minutes. Aerosols of LPS are generated by a nebuliser (DeVilbiss, USA) and this is directed into the Perspex exposure chamber. Following the 15-minute LPS-exposure period, the animals are returned to the holding cages and allowed free access to both food and water.

[In an alternative embodiment, the rats can exposed to LPS less than 2 hours after i.t. dosing. In another alternative embodiment, the rats can exposed to LPS more than 2 hours (e.g. ca. 4 or ca. 6 hours) after i.t. dosing by vehicle or PDE4 inhibitor, to test whether or not the PDE4 inhibitor has a long duration of action (which is not essential).]

Bronchoalveolar lavage: 4 hours after LPS exposure the animals are killed by overdose of sodium pentobarbitone (i.p.). The trachea is cannulated with polypropylene tubing and the lungs are lavaged (washed out) with 3 x 5 mls of heparinised (25 $units.ml^{-1}$) phosphate buffered saline (PBS).

Neutrophil cell counts: The Bronchoalveolar lavage (BAL) samples are centrifuged at 1300 rpm for 7 minutes. The supernatant is removed and the resulting cell pellet resuspended in 1 ml PBS. A cell slide of the resuspension fluid is prepared by placing 100µl of resuspended BAL fluid into cytospin holders and then is spun at 5000 rpm for 5 minutes. The slides are allowed to air dry and then stained with Leishmans stain (20 minutes) to allow differential cell counting. The total cells are also counted from the resuspension. From these two counts, the total numbers of neutrophils in the BAL are determined. For a measure of PDE4-inhibitor-induced inhibition of neutrophilia, a comparison of the neutrophil count in rats treated with vehicle and rats treated with PDE4 inhibitors is conducted.

By varying the dose of the PDE4 inhibitor used in the dosing step (e.g. 0.2 or 0.1 mg of PDE4 inhibitor per kg of body weight, down to e.g. 0.01 mg/kg), a dose-response curve can be generated.

In Vivo Assay 4. Evaluation of Therapeutic Index of Orally-administered PDE 4 inhibitors in the conscious ferret

1.1 Materials

The following materials are used for these studies:

PDE4 inhibitors are prepared for oral (p.o.) administration by dissolving in a fixed volume (1 ml) of acetone and then adding cremophor to 20% of the final volume. Acetone is evaporated by directing a flow of nitrogen gas onto the solution. Once the acetone is removed, the solution is made up to final volume with distilled water. LPS is dissolved in phosphate buffered saline.

1.2 Animals

Male ferrets (Mustela Pulorius Furo, weighing 1 – 2 kg) are transported and allowed to acclimatise for not less than 7 days. The diet comprises SDS diet C pelleted food given *ad lib* with Whiskers^{TM} cat food given 3 times per week. The animals are supplied with pasteurised animal grade drinking water changed daily.

1.3 Experimental Protocol(s)

1.3.1 Dosing with PDE4 inhibitors

PDE4 inhibitors are administered orally (p.o.), using a dose volume of 1ml/kg. Ferrets are fasted overnight but allowed free access to water. The animals are orally dosed with vehicle or PDE 4 inhibitor using a 15cm dosing needle that is passed down the back of the throat into the oesophagus. After dosing, the animals are returned to holding cages fitted with perspex doors to allow observation, and given free access to water. The animals are constantly observed and any emetic episodes (retching and vomiting) or behavioural changes are recorded. The animals are allowed access to food 60 – 90 minutes after p.o. dosing.

1.3.2 Exposure to LPS

Thirty minutes after oral dosing with compound or vehicle control, the ferrets are placed into sealed perspex containers and exposed to an aerosol of LPS (30 μg/ml) for 10 minutes. Aerosols of LPS are generated by a nebuliser (DeVilbiss, USA) and this is directed into the perspex exposure chamber. Following a 10-minute exposure period, the animals are returned to the holding cages and allowed free access to water, and at a later stage, food. General observation of the animals continues for a period of at least 2.5 hours post oral dosing. All emetic episodes and behavioural changes are recorded.

1.3.3 Bronchoalveolar lavage and cell counts

Six hours after LPS exposure the animals are killed by overdose of sodium pentobarbitone administered intraperitoneally. The trachea is then cannulated with polypropylene tubing and the lungs lavaged twice with 20 ml heparinised (10 units/ml) phosphate buffered saline (PBS). The bronchoalveolar lavage (BAL) samples are centrifuged at 1300 rpm for 7 minutes. The supernatant is removed and the resulting cell pellet re-suspended in 1 ml PBS. A cell smear of re-suspended fluid is prepared and stained with Leishmans stain to allow differential cell counting. A total cell count is made using the remaining re-suspended sample. From this, the total number of neutrophils in the BAL sample is determined.

1.3.4 Pharmacodynamic readouts

The following parameters are recorded:
a) % inhibition of LPS-induced pulmonary neutrophilia to determine the dose of PDE4 inhibitor which gives 50% inhibition (D50).
b) Emetic episodes – the number of vomits and retches are counted to determine the dose of PDE4 inhibitor that gives a 20% incidence of emesis (D20).
c) A therapeutic index (TI), using this assay, is then calculated for each PDE4 inhibitor using the following equation:

$$\text{Ferret Therapeutic index (TI) (D20/D50)} = \frac{\text{D20 incidence of emesis in ferret}}{\text{D50 inhibition of neutrophilia in ferret}}$$

It is noted that the Ferret Therapeutic index (TI) (D20/D50) calculated using this in vivo Assay 4 is often substantially different to, and for example is often substantially lower than, the Rat TI (50/50) calculated using the rat oral inflammation and pica feeding Assays 1+2.

The calculation of Ferret TI using the known PDE4 inhibitor roflumilast in this Assay 4 is:
D20 for emesis = about 0.46 mg/kg p.o.,
D50 for ferret neutroplilia = about 0.42 mg/kg p.o.,
Ferret TI = about 1.1.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "Intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

Abbreviations used herein:

DMSO	dimethyl sulfoxide
DCM	dichloromethane
EtOAc	ethyl acetate
Et_2O	diethyl ether
DMF	dimethyl formamide
MeOH	methanol
HPLC	high pressure liquid chromatography
SPE	solid phase extraction
NMR	nuclear magnetic resonance (in which: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, H = no. of protons)
LCMS	liquid chromatography/mass spectroscopy
TLC	thin layer chromatography
BEMP	2-t-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphazine
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBT	hydroxybenzotriazole = 1-hydroxybenzotriazole
h	hours
DIPEA	diisopropylethyl amine ($^iPr_2NEt$)
T_{RET}	retention time (from LCMS)
THF	Tetrahydrofuran
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide
Room temperature	this is usually in the range of about 20 to about 25 °C.

Abbreviations used herein:

AcOH	acetic acid
Ac_2O	acetic anhydride
BOC_2O	di tert-butyl carbonate
DMSO	dimethyl sulfoxide
DCM	dichloromethane

DMF	dimethyl formamide
DIPEA	diisopropylethyl amine ($^{i}Pr_2NEt$)
EtOAc	ethyl acetate
Et_2O	diethyl ether
Et_3N	triethylamine
EtOH	ethanol
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
MeCN	acetonitrile
MeOH	methanol
THF	Tetrahydrofuran
HPLC	high pressure liquid chromatography
SPE	solid phase extraction
NMR	nuclear magnetic resonance (in which: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, H = no. of protons)
LCMS	liquid chromatography/mass spectroscopy
TLC	thin layer chromatography
h	hours
T_{RET}	retention time
Room temperature	this is usually in the range of about 20 to about 25 °C.

General Experimental Details

Machine Methods used herein:

LCMS (liquid chromatography/mass spectroscopy)

Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nM
Column : 3.3cm x 4.6mm ID, 3µm ABZ+PLUS
Flow Rate : 3ml/min
Injection Volume : 5µl
Solvent A : 95% acetonitrile + 0.05% formic acid
Solvent B : 0.1% formic acid + 10mMolar ammonium acetate
Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min
It should be noted that retention times (T_{RET}) quoted herein may vary slightly (+/- 0.1min.) when samples were run on different Waters machines, even though the same type of column and identical flow rates, injection volumes, solvents and gradients were used.

Mass directed autoprep HPLC

The prep column used was a Supelcosil ABZplus (10cm x 2.12cm)

(usually 10cm x 2.12cm x 5 μm).
UV wavelength : 200-320nM
Flow : 20ml/min
Injection Volume: 1ml; or more preferably 0.5 ml
Solvent A : 0.1% formic acid
Solvent B : 95% acetonitrile + 5% formic acid; or more usually 99.95% acetonitrile + 0.05% formic acid
Gradient : 100% A/1min, 100-80% A/9min, 80-1% A/3.5min, 1% A/1.4min, 1-100%A/0.1min

Chiral Columns for Chromatographic Purification

ChiralPak AD and ChiralCel OD columns were obtained from:
Chiral Technologies Europe Sarl, Illkirch, France (Telephone: 0033(0)388795200; (cte@chiral.fr; www.chiral.fr).
Whelk-01 columns were purchased from: Hichrom, 1, The Markham Centre, Station Road, Theale, Reading, Berks. RG7.4PE, United Kingdom (Telephone: 0044(0)1189303660; (info@hichrom.co.uk; www.hichrom.co.uk). Hichrom are agents for the manufacturers Regis Technologies Inc., 8210 Austin Avenue, Morton Grove, IL60053, USA; telephone: 847-967-6000; www.registech.com.

Intermediates and Examples

All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich. The addresses of the suppliers for some of the starting materials mentioned in the Intermediates and Examples below or the Assays above are as follows:

- ABCR GmbH & CO. KG, P.O. Box 21 01 35, 76151 Karlsruhe, Germany
- Aceto Color Intermediates (catalogue name), Aceto Corporation, One Hollow Lane, Lake Success, NY, 11042-1215, USA
- Acros Organics, A Division of Fisher Scientific Company, 500 American Road, Morris Plains, NJ 07950, USA
- Apin Chemicals Ltd., 82 C Milton Park, Abingdon, Oxon OX14 4RY, United Kingdom
- Apollo Scientific Ltd., Unit 1A, Bingswood Industrial Estate, Whaley Bridge, Derbyshire SK23 7LY, United Kingdom
- Aldrich (catalogue name), Sigma-Aldrich Company Ltd., Dorset, United Kingdom, telephone: +44 1202 733114; Fax: +44 1202 715460; ukcustsv@eurnotes.sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; telephone: 314-771-5765; fax: 314-771-5757; custserv@sial.com; or

- Aldrich (catalogue name), Sigma-Aldrich Chemie Gmbh, Munich, Germany; telephone: +49 89 6513 0; Fax: +49 89 6513 1169; deorders@eurnotes.sial.com.
- Alfa Aesar, A Johnson Matthey Company, 30 Bond Street, Ward Hill, MA 01835-8099, USA
- Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8 4SP, United Kingdom
- Array Biopharma Inc., 1885 33rd Street, Boulder, CO 80301, USA
- AstaTech, Inc., 8301 Torresdale Ave., 19C, Philadelphia, PA 19136, USA
- Austin Chemical Company, Inc., 1565 Barclay Blvd., Buffalo Grove, IL 60089, USA
- Avocado Research, Shore Road, Port of Heysham Industrial Park, Heysham Lancashire LA3 2XY, United Kingdom
- Bayer AG, Business Group Basic and Fine Chemicals, D-51368 Leverkusen, Germany
- Berk Univar plc, Berk House, P.O.Box 56, Basing View, Basingstoke, Hants RG21 2E6, United Kingdom
- Butt Park Ltd., Braysdown Works, Peasedown St. John, Bath BA2 8LL, United Kingdom
- Chemical Building Blocks (catalogue name), Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France
- ChemBridge Europe, 4 Clark's Hill Rise, Hampton Wood, Evesham, Worcestershire WR11 6FW, United Kingdom
- ChemService Inc., P.O.Box 3108, West Chester, PA 19381, USA
- Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA
- Dynamit Nobel GmbH, Germany; also available from: Saville Whittle Ltd (UK agents of Dynamit Nobel), Vickers Street, Manchester M40 8EF, United Kingdom
- E. Merck, Germany; or E. Merck (Merck Ltd), Hunter Boulevard, Magna Park, Lutterworth, Leicestershire LE17 4XN, United Kingdom
- Esprit Chemical Company, Esprit Plaza, 7680 Matoaka Road, Sarasota, FL 34243, USA
- Exploratory Library (catalogue name), Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France
- Fluka Chemie AG, Industriestrasse 25, P.O. Box 260, CH-9471 Buchs, Switzerland
- Fluorochem Ltd., Wesley Street, Old Glossop, Derbyshire SK13 7RY, United Kingdom
- ICN Biomedicals, Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, USA
- Interchim Intermediates (catalogue name), Interchim, 213 Avenue Kennedy, BP 1140, Montlucon, Cedex, 03103, France
- Key Organics Ltd., 3, Highfield Indusrial Estate, Camelford, Cornwall PL32 9QZ, United Kingdom
- Lancaster Synthesis Ltd., Newgate, White Lund, Morecambe, Lancashire LA3 3DY, United Kingdom
- Manchester Organics Ltd., Unit 2, Ashville Industrial Estate, Sutton Weaver, Runcorn, Cheshire WA7 3PF, United Kingdom
- Matrix Scientific, P.O. Box 25067, Columbia, SC 29224-5067, USA
- Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom
- Maybridge Reactive Intermediates (catalogue name), Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom
- MicroChemistry Building Blocks (catalogue name), MicroChemistry-RadaPharma, Shosse Entusiastov 56, Moscow, 111123, Russia

- Miteni S.p.A., Via Mecenate 90, Milano, 20138, Italy
- Molecular Devices Corporation, Sunnydale, CA, USA
- N.D. Zelinsky Institute, Organic Chemistry, Leninsky prospect 47, 117913 Moscow B-334, Russia
- Optimer Building Block (catalogue name), Array BioPharma, 3200 Walnut Street, Boulder, CO 80301, USA
- Peakdale Molecular Ltd., Peakdale Science Park, Sheffield Road, Chapel-en-le-Frith, High Peak SK23 0PG, United Kingdom
- Pfaltz & Bauer, Inc., 172 East Aurora Street, Waterbury, CT 06708, USA
- Rare Chemicals (catalogue name), Rare Chemicals GmbH, Schulstrasse 6, 24214 Gettorf, Germany
- SALOR (catalogue name) (Sigma Aldrich Library of Rare Chemicals), Aldrich Chemical Company Inc, 1001 West Saint Paul Avenue, Milwaukee, WI 53233, USA
- Sigma (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; see "Aldrich" above for other non-US addresses and other contact details
- SIGMA-RBI, One Strathmore Road, Natick, MA 01760-1312, USA
- Synchem OHG Heinrich-Plett-Strasse 40, Kassel, D-34132, Germany
- Syngene International Pvt Ltd, Hebbagodi, Hosur Road, Bangalore, India.
- TCI America, 9211 North Harborgate Street, Portland, OR 97203, USA
- TimTec Building Blocks A, TimTec, Inc., P O Box 8941, Newark, DE 19714-8941, USA
- Trans World Chemicals, Inc., 14674 Southlawn Lane, Rockville, MD 20850, USA
- Ubichem PLC, Mayflower Close, Chandlers Ford Industrial Estate, Eastleigh, Hampshire SO53 4AR, United Kingdom
- Ultrafine (UFC Ltd.), Synergy House, Guildhall Close, Manchester Science Park, Manchester M15 6SY, United Kingdom

- ACB Blocks Ltd; Kolokolnikov Per, 9/10 Building 2, Moscow, 103045, Russia
- Acros Organics, A Division of Fisher Scientific Company, 500 American Road, Morris Plains, NJ 07950, USA
- Aldrich (catalogue name), Sigma-Aldrich Company Ltd., Dorset, United Kingdom, telephone: +44 1202 733114; Fax: +44 1202 715460; ukcustsv@eurnotes.sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; telephone: 314-771-5765; fax: 314-771-5757; custserv@sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Chemie Gmbh, Munich, Germany; telephone: +49 89 6513 0; Fax: +49 89 6513 1169; deorders@eurnotes.sial.com.
- Arch Corporation, 100 Jersey Avenue, Building D, New Brunswick, NJ08901, USA
- Avocado Research, Shore Road, Port of Heysham Industrial Park, Heysham Lancashire LA3 2XY, United Kingdom
- Bionet Research Ltd; Highfield Industrial Estate, Camelford, Cornwall PL32 9QZ UK
- ChemBridge Europe, 4 Clark's Hill Rise, Hampton Wood, Evesham, Worcestershire WR11 6FW, United Kingdom
- CiventiChem, PO Box 12041, Research Triangle Park, NC 27709, USA

- Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA
- Exploratory Library (catalogue name), Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France
- Fluka Chemie AG, Industriestrasse 25, P.O. Box 260, CH-9471 Buchs, Switzerland
- Fluorochem Ltd., Wesley Street, Old Glossop, Derbyshire SK13 7RY, United Kingdom
- Interchim Intermediates (catalogue name), Interchim, 213 Avenue Kennedy, BP 1140, Montlucon, Cedex, 03103, France
- Lancaster Synthesis Ltd., Newgate, White Lund, Morecambe, Lancashire LA3 3DY, United Kingdom
- Maybridge Combichem (catalogue name), Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom
- MicroChemistry Building Blocks (catalogue name), MicroChemistry-RadaPharma, Shosse Entusiastov 56, Moscow, 111123, Russia
- Omega Chem,
- Peakdale Molecular Ltd., Peakdale Science Park, Sheffield Road, Chapel-en-le-Frith, High Peak SK23 0PG, United Kingdom
- SALOR (catalogue name) (Sigma Aldrich Library of Rare Chemicals), Aldrich Chemical Company Inc, 1001 West Saint Paul Avenue, Milwaukee, WI 53233, USA
- Sigma (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; see "Aldrich" above for other non-US addresses and other contact details
- TCI America, 9211 North Harborgate Street, Portland, OR 97203, USA
- TimTec Building Blocks B, TimTec, Inc., P O Box 8941, Newark, DE 19714-8941, USA
- TimTec Stock Library, TimTec, Inc., P O Box 8941, Newark, DE 19714-8941, USA

Table of Intermediates

Inter-mediate Number	Name
1	Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
2	4-Aminotetrahydropyran
3	1-Acetyl-4-aminopiperidine
4	Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
5	ethyl 4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
6	Ethyl 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
7	Ethyl 1-ethyl-4-[(4-hydroxycyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
8	Ethyl 1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
9	Ethyl 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
10	Ethyl 4-chloro-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate

11	Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
12	Ethyl 1-ethyl-4-{[(1*SR*,3*RS*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
13	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
14	4-(Cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
15	4-[(1-Acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
16	1-Ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
17	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
18	1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
19	1-Ethyl-4-{[(1*SR*,3*RS*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
20	*N*-[(1*E*)-(2,4-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide
21	2-methyl-*N*-[(1*E*)-(2-methylphenyl)methylidene]-2-propanesulfinamide
22	*N*-[(1*E*)-(3-hydroxyphenyl)methylidene]-2-methyl-2-propanesulfinamide
23	2-methyl-*N*-{(1*E*)-[3-(methyloxy)phenyl]methylidene}-2-propanesulfinamide
24	2-methyl-*N*-{(1*E*)-[4-(methyloxy)phenyl]methylidene}-2-propanesulfinamide
25	*N*-[(1*E*)-(4-bromophenyl)methylidene]-2-methyl-2-propanesulfinamide
26	2-methyl-*N*-[(1*E*)-(4-methylphenyl)methylidene]-2-propanesulfinamide
27	*N*-{(1*E*)-[4-(ethyloxy)phenyl]methylidene}-2-methyl-2-propanesulfinamide
28	2-methyl-*N*-{(1*E*)-[4-(propyloxy)phenyl]methylidene}-2-propanesulfinamide
29	*N*-((1*E*)-{4-[(difluoromethyl)oxy]phenyl}methylidene)-2-methyl-2-propanesulfinamide
30	2-methyl-*N*-{(1*E*)-[4-(trifluoromethyl)phenyl]methylidene}-2-propanesulfinamide
31	2-methyl-*N*-{(1*E*)-[4-(1-methylethyl)phenyl]methylidene}-2-propanesulfinamide
32	*N*-[(1*E*)-(2,3-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide
33	*N*-[(1*E*)-(4-chloro-2-fluorophenyl)methylidene]-2-methyl-2-propanesulfinamide
34	*N*-[(1*Z*)-(3,4-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide
35	*N*-[(1*E*)-(3,5-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide
36	N-[(1E)-(3-chloro-4-methylphenyl)methylidene]-2-methyl-2-propanesulfinamide

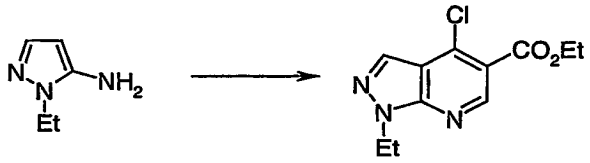
37	*N*-[1-(2,4-dimethylphenyl)ethyl]-2-methyl-2-propanesulfinamide
38	2-methyl-*N*-[1-(2-methylphenyl)ethyl]-2-propanesulfinamide
39	*N*-{1-[4-(ethyloxy)phenyl]ethyl}-2-methyl-2-propanesulfinamide
40	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-2-methyl-2-propanesulfinamide
41	2-methyl-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-2-propanesulfinamide
42	*N*-[1-(2,3-dimethylphenyl)ethyl]-2-methyl-2-propanesulfinamide
43	*N*-[1-(4-chloro-2-fluorophenyl)ethyl]-2-methyl-2-propanesulfinamide
44	*N*-[1-(3-chloro-4-methylphenyl)ethyl]-2-methyl-2-propanesulfinamide
45	2-methyl-*N*-[1-(2-methylphenyl)propyl]-2-propanesulfinamide
46	*N*-[1-(3-hydroxyphenyl)propyl]-2-methyl-2-propanesulfinamide
47	2-methyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-2-propanesulfinamide
48	2-methyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-2-propanesulfinamide
49	*N*-[1-(4-bromophenyl)propyl]-2-methyl-2-propanesulfinamide
50	2-methyl-*N*-[1-(4-methylphenyl)propyl]-2-propanesulfinamide
51	*N*-{1-[4-(ethyloxy)phenyl]propyl}-2-methyl-2-propanesulfinamide
52	2-methyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-2-propanesulfinamide
53	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-2-methyl-2-propanesulfinamide
54	2-methyl-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-2-propanesulfinamide
55	2-methyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-2-propanesulfinamide
56	*N*-[1-(2,3-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide
57	*N*-[1-(2,4-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide
58	*N*-[1-(4-chloro-2-fluorophenyl)propyl]-2-methyl-2-propanesulfinamide
59	*N*-[1-(3,4-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide
60	*N*-[1-(3,5-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide
61	*N*-[1-(3-chloro-4-methylphenyl)propyl]-2-methyl-2-propanesulfinamide
62	[1-(2,4-dimethylphenyl)ethyl]amine hydrochloride
63	[1-(2-methylphenyl)ethyl]amine hydrochloride
64	{1-[4-(ethyloxy)phenyl]ethyl}amine hydrochloride
65	(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)amine hydrochloride
66	{1-[4-(trifluoromethyl)phenyl]ethyl}amine hydrochloride
67	[1-(2,4-dimethylphenyl)ethyl]amine trifluoroacetate
68	[1-(4-chloro-2-fluorophenyl)ethyl]amine hydrochloride
69	[1-(3-chloro-4-methylphenyl)ethyl]amine hydrochloride
70	[1-(2-methylphenyl)propyl]amine hydrochloride
71	3-(1-aminopropyl)phenol hydrochloride
72	{1-[3-(methyloxy)phenyl]propyl}amine hydrochloride
73	{1-[4-(methyloxy)phenyl]propyl}amine hydrochloride
74	[1-(4-bromophenyl)propyl]amine hydrochloride
75	[1-(4-methylphenyl)propyl]amine hydrochloride
76	{1-[4-(ethyloxy)phenyl]propyl}amine hydrochloride
77	{1-[4-(propyloxy)phenyl]propyl}amine hydrochloride

78	(1-{4-[(difluoromethyl)oxy]phenyl}propyl)amine hydrochloride
79	{1-[4-(trifluoromethyl)phenyl]propyl}amine hydrochloride
80	{1-[4-(1-methylethyl)phenyl]propyl}amine hydrochloride
81	[1-(2,3-dimethylphenyl)propyl]amine hydrochloride
82	[1-(2,4-dimethylphenyl)propyl]amine hydrochloride
83	[1-(4-chloro-2-fluorophenyl)propyl]amine hydrochloride
84	[1-(3,4-dimethylphenyl)propyl]amine hydrochloride
85	[1-(3,5-dimethylphenyl)propyl]amine hydrochloride
86	[1-(3-chloro-4-methylphenyl)propyl]amine hydrochloride
87	[1-(3,5-dimethylphenyl)ethyl]amine hydrochloride
88	3-(1-aminoethyl)phenol hydrochloride
89	{1-[4-(1-methylethyl)phenyl]ethyl}amine hydrochloride
90	[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]amine hydrochloride
91	[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]amine hydrochloride
92	(2,2,2-trifluoro-1-phenylethyl)amine hydrochloride
93	[1-(4-bromophenyl)-2,2,2-trifluoroethyl]amine hydrochloride
94	{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}amine hydrochloride
95	(1-phenylhexyl)amine hydrochloride
96	(1-phenylpentyl)amine hydrochloride
97	[cyclopropyl(phenyl)methyl]amine hydrochloride
98	(2-methyl-1-phenylpropyl)amine hydrochloride
99	(1-phenylbutyl)amine hydrochloride
100	[1-(2,4-dimethylphenyl)ethyl]amine trifluoroacetate
101	[1-(2,4-dimethylphenyl)ethyl]amine trifluoroacetate
102	Ethyl 4-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
103	Ethyl 1-ethyl-4-(4-piperidinylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate hydrochloride
104	Ethyl 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
105	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
106	4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
107	4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride
108	4-chloro-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
109	4-chloro-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
110	1,1-dimethylethyl [1-(aminocarbonyl)-4-piperidinyl]carbamate
111	4-amino-1-piperidinecarboxamide hydrochloride

112	1,1-dimethylethyl [4-(aminocarbonyl)cyclohexyl]carbamate
113	4-aminocyclohexanecarboxamide hydrochloride

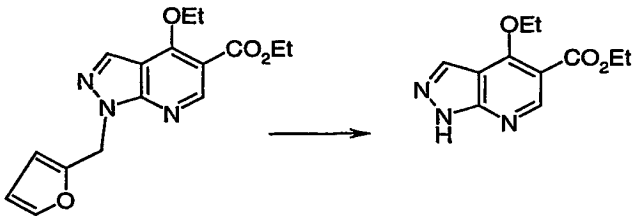
Intermediate 1: Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

Prepared from commercially available 5-amino-1-ethyl pyrazole as described by G. Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027:



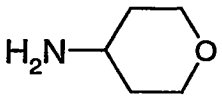
Intermediate 1A: Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

Can be prepared by oxidative cleavage (SeO_2) of 1-furanylmethyl derivative, as described by T. M. Bare *et. al.* In *J. Med. Chem.*, 1989, 32, 2561-2573, (further referenced to Zuleski, F. R., Kirkland, K. R., Melgar, M. D.; Malbica, *J. Drug. Metab. Dispos.*, 1985, 13, 139)

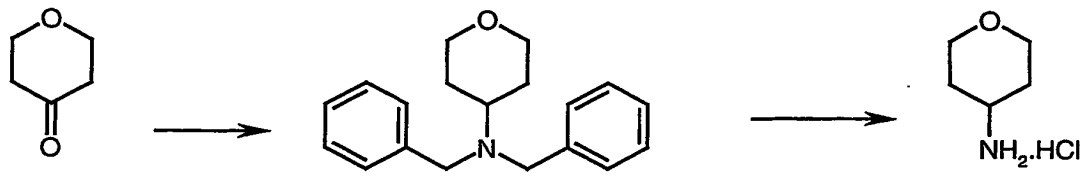


Intermediate 2: 4-Aminotetrahydropyran

Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA (CAS 38041-19-9)



Intermediate 2A: Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride



Step1: N,N-dibenzyltetrahydro-2H-pyran-4-amine

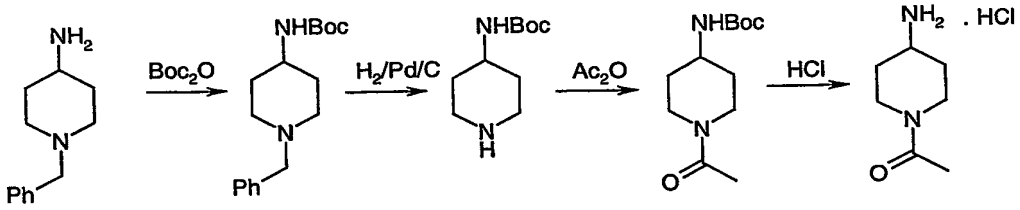
Dibenzylamine (34.5g) and acetic acid (6.7ml) were added to a stirred solution of tetrahydro-4H-pyran-4-one (16.4g, commercially available from e.g. Aldrich) in dichloromethane (260ml) at 0 °C to 5 °C. After 2.5h at 0 °C to 5 °C, sodium triacetoxyborohydride (38.9g) was added portionwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction mixture was washed successively with 2M-sodium hydroxide (200ml and 50ml), water (2 x 50ml) and brine (50ml), then dried and evaporated to give a yellow oil (45g). This oil was stirred with methanol (50ml) at 4 °C for 30min to give the product as a white solid (21.5g). LCMS showed $MH^+ = 282$; $T_{RET} = 1.98$ min.

Step 2: Tetrahydro-2H-pyran-4-amine hydrochloride

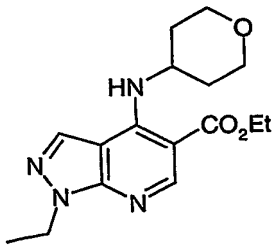
N,N-dibenzyltetrahydro-2*H*-pyran-4-amine (20.5g) was dissolved in ethanol (210ml) and hydrogenated over 10% palladium on carbon catalyst (4g) at 100 psi for 72h at room temperature. The reaction mixture was filtered and the filtrate was adjusted to pH 1 with 2M-hydrogen chloride in diethyl ether. Evaporation of solvents gave a solid which was triturated with diethyl ether to give the product as a white solid (9.23g). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 8.24 (br. s, 3H), 3.86 (dd, 12, 4Hz, 2H), 3.31 (dt, 2, 12Hz, 2H), 3.20 (m, 1H), 1.84 (m, 2H), 1.55 (dq, 4, 12Hz, 2H).

Intermediate 3: 1-Acetyl-4-aminopiperidine

Prepared from commercially available N1-benzyl-4-aminopiperidine as described by Yamada *et. al.* In WO 00/42011:



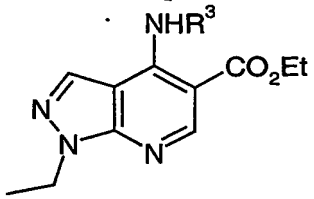
Intermediate 4: Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

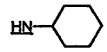
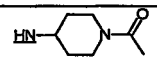


Intermediate 1 (0.20g) and triethylamine (0.55ml) were suspended in ethanol (8ml) and 4-aminotetrahydropyran (Intermediate 2, 0.088g) was added. The mixture was stirred under nitrogen and heated at 80°C for 16h, then concentrated *in vacuo*. The residue was

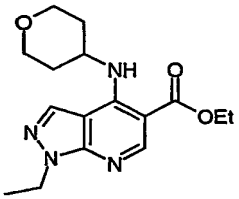
partitioned between DCM and water. The layers were separated and the organic layer was loaded directly onto an SPE cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O and (v) EtOAc. Fractions containing desired material were combined and concentrated *in vacuo* to afford Intermediate 4 (0.21g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.93$min.

Similarly prepared from Intermediate 1 were the following:



	NHR^3	Amine reagent	MH^+ ion	T_{RET} (min)
Intermediate 5		Cyclohexylamine	317	3.65
Intermediate 6		Intermediate 3	360	2.71

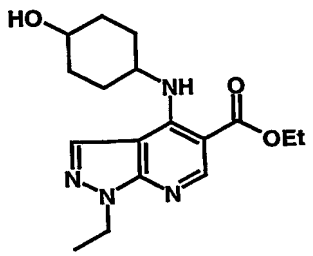
Intermediate 4



Alternative synthesis: Instead of the method shown above Intermediate 4 can also be made using the following Method B:

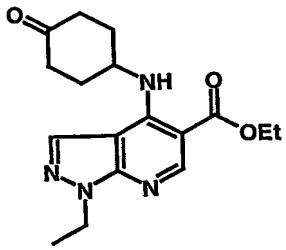
Method B: Intermediate 1 (2.5g) was dissolved in acetonitrile (15ml). 4-Aminotetrahydropyran hydrochloride (Intermediate 2A) (1.1g) and N,N-diisopropylethylamine (9.4ml) were added and the mixture stirred under nitrogen at 85 °C for 16h. A trace of starting material remained, so an additional portion of 4-aminotetrahydropyran hydrochloride (0.11g) was added and stirring continued at 85 °C for a further 16h. The mixture was then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was washed with further water (2x20ml) then dried (Na_2SO_4) and concentrated in vacuo. The residue was further purified by chromatography using Biotage (silica, 90g), eluting with cyclohexane : ethyl acetate to afford Intermediate 4 (2.45g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.90$min.

Intermediate 7: Ethyl 1-ethyl-4-[(4-hydroxycyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



Intermediate 1 (1.5g, 5.9mmol) was dissolved in MeCN (80ml). Trans-4-aminocyclohexanol (0.817g, 7.1mmol, commercially available from TCI-America; alternatively (e.g. as the HCl salt) from Aldrich) and DIPEA (6.18ml, 35.5mmol) were added and the mixture was stirred at 85°C for 16h. The mixture was concentrated *in vacuo*, and the residue was partitioned between DCM (120ml) and water (30ml). The phases were separated and the organic phase was dried (Na_2SO_4) and evaporated to give a pale yellow solid. The solid was dissolved in a mixture of DCM (10ml) and chloroform (3ml), and applied in equal portions to two SPE cartridges (silica, 20g) which were eluted sequentially with a gradient of EtOAc:cyclohexane (1:16, then 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing the desired material were combined and evaporated *in vacuo* to give Intermediate 7 (1.89g) as a white solid. LCMS showed $MH^+ = 333$; $T_{RET} = 2.79$min.

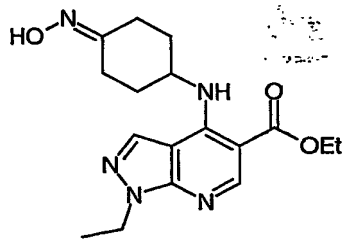
Intermediate 8: Ethyl 1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



Intermediate 7 (1.893g, 5.7mmol) was suspended in acetone (12ml) and the stirred suspension was treated at 0°C with Jones reagent (1.81ml). After 30min, a further quantity of Jones reagent (1.81ml) was added to the reaction mixture which was maintained at 0°C. After a further 2h, a final portion of Jones reagent (1.44ml) was added to the reaction mixture, and stirring at 0°C was continued for 1h. Isopropanol (3.8ml) was added to the reaction mixture, followed by water (15ml). The resulting mixture was extracted with EtOAc (2 x 40ml). The combined organic extracts were washed with water (8ml), dried (Na_2SO_4) and evaporated to a grey solid. The solid was dissolved in DCM (10ml) and applied in equal portions to two SPE cartridges (silica, 20g) which were

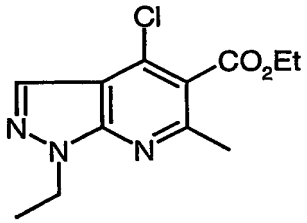
eluted sequentially with a gradient of EtOAc:cyclohexane (1:16, then 1:8, 1:4, 1:2, and 1:1). Fractions containing the desired material were combined and evaporated *in vacuo* to give Intermediate 8 (1.893g) as a white solid. LCMS showed MH^+ = 331; T_{RET} = 2.84min.

Intermediate 9: Ethyl 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



A mixture of Intermediate 8 (200mg), hydroxylamine hydrochloride (50mg) and anhydrous potassium carbonate (420mg) in MeCN(10 ml) was stirred and heated at reflux for 17 hours. The solution was cooled and concentrated *in vacuo*. The residue was partitioned between EtOAc and water. The organic phase was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give Intermediate 9 as a white powder (203mg). LCMS showed MH^+ = 346; T_{RET} = 2.84min.

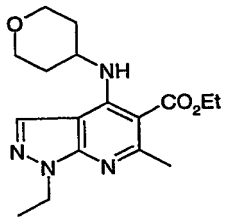
Intermediate 10: Ethyl 4-chloro-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



A mixture of 5-amino-1-ethylpyrazole (1.614g, 14.5mmol) and diethyl 2-(1-ethoxyethylidene)malonate (3.68g, 16.0mmol, as described by P.P.T. Sah, *J. Amer. Chem. Soc.*, 1931, 53, 1836) was heated at 150 °C under Dean Stark conditions for 5 hours. Phosphorous oxychloride (25ml) was carefully added to the mixture and the resulting solution was heated at 130 °C under reflux for 18 hours. The mixture was concentrated *in vacuo*, then the residual oil was carefully added, with cooling, to water (100ml). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was purified by Biotage chromatography (silica, 90g) eluting with EtOAc-petroleum ether (1:19). Fractions containing the desired product were combined and

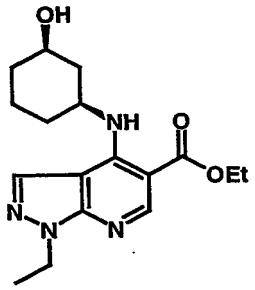
concentrated *in vacuo* to afford Intermediate 10 (1.15g). LCMS showed $MH^+ = 268$; $T_{RET} = 3.18$min.

Intermediate 11: Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



4-Aminotetrahydropyran hydrochloride (Intermediate 2, 0.413g, 3.0mmol) was added to a mixture of Intermediate 10 (0.268g, 1.0mmol) and DIPEA (0.87ml, 5.0mmol) in MeCN (3ml). The resulting mixture was heated at 85 °C for 24 hours. Volatiles were removed *in vacuo* and the residue was dissolved in chloroform (1.5ml) and applied to a SPE cartridge (silica, 5g). The cartridge was eluted successively with Et_2O, EtOAc and EtOAc-MeOH (9/1). Fractions containing the desired product were combined and concentrated *in vacuo* to give the desired product contaminated with starting material (Intermediate 10). Further purification using a SPE cartridge (silica, 5g) eluting with EtOAc-cyclohexane (1:3) afforded Intermediate 11 (0.248g). LCMS showed $MH^+ = 333$; $T_{RET} = 2.75$min.

Intermediate 12: Ethyl 1-ethyl-4-{[(1*SR*,3*RS*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate

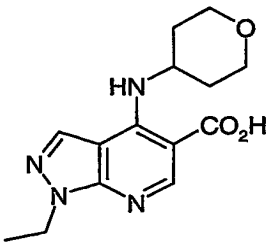


[*cis*-(3-hydroxycyclohex-1-yl)amino group, racemic]

3-Aminocyclohexanol (0.677g, 5.9mmol, as described in *J. Chem. Soc., Perkin Trans 1*, 1994, 537) in MeCN(10ml) and EtOH (1ml) was added at room temperature to a stirred solution of Intermediate 1 (1.24g, 4.9mmol) and DIPEA (4.26ml, 24.5mmol) in MeCN (25ml). The resulting mixture was stirred at 85°C for 17h. The mixture was concentrated *in vacuo*, and the residue was partitioned between DCM (50ml) and water (10ml). The phases were separated and the organic phase was dried (Na_2SO_4) and evaporated to give an orange-brown oil. The oil was purified by Biotage chromatography (silica 100g)

eluting with 30-50% EtOAc in cyclohexane to give Intermediate 12 as a white foam (0.68g). LCMS showed $MH^+ = 333$; $T_{RET} = 2.76$min.

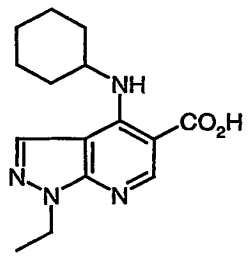
Intermediate 13: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 4 (0.21g) in ethanol : water (95:5, 10ml) was treated with sodium hydroxide (0.12g). The mixture was heated at 50 °C for 8h, then concentrated *in vacuo*, dissolved in water and acidified to pH 4 with acetic acid. The resultant white solid was removed by filtration and dried *in vacuo* to afford Intermediate 13 as an off-white solid (0.156g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.11$min.

An alternative preparation of Intermediate 13 is as follows:
A solution of Intermediate 4 (37.8g) in ethanol : water (4:1, 375ml) was treated with sodium hydroxide (18.9g). The mixture was heated at 50 °C for 5 hours, then concentrated *in vacuo*, dissolved in water and acidified to pH 2 with aqueous hydrochloric acid (2M). The resultant white solid was removed by filtration and dried *in vacuo* to afford Intermediate 13 as an off-white solid (29.65g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.17$ min.

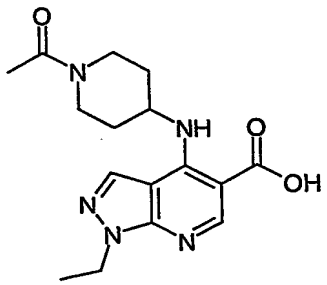
Intermediate 14: 4-(Cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A solution of Intermediate 5 (5.37g, 17mmol) in EtOH (30ml) was treated with a solution of sodium hydroxide (2.72g, 68mmol) in water (20ml), and the resulting mixture was stirred at 50°C for 3h. The reaction mixture was concentrated *in vacuo*, dissolved in water (250ml) and the cooled solution was acidified to pH 1 with 5M-hydrochloric acid. The

resultant solid was collected by filtration and dried *in vacuo* to afford Intermediate 14 as a white solid (4.7g). LCMS showed $MH^+ = 289$; $T_{RET} = 2.83$min.

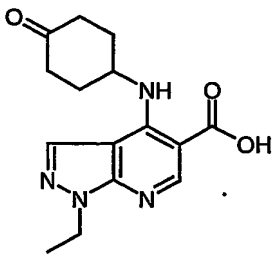
Intermediate 15: 4-[(1-Acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



Aqueous sodium hydroxide solution (8.55ml, 2M) was added to a solution of Intermediate 6 (1.55g) in EtOH (13ml). The mixture was heated at 50 °C for 18h then neutralised using aqueous hydrochloric acid and evaporated *in vacuo* to afford a mixture of 1-ethyl-4-(4-piperidinylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid and 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid

Acetic acid (0.36ml) was added to a stirred mixture of HATU (2.41g) and DIPEA (2.21ml) in DMF (65ml). After stirring for 15 min the mixture was added to the mixture of 1-ethyl-4-(4-piperidinylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid and 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid and the reaction mixture was stirred for 15h. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography using Biotage (silica 90g), eluting with DCM : MeOH (0% - 5% MeOH) to afford Intermediate 15 (1.36g) as a white solid. LCMS showed MH^+ 334; $T_{RET} = 2.06$ min.

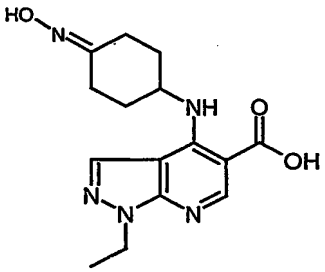
Intermediate 16: 1-Ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A solution of sodium hydroxide (0.053g, 1.32mmol) in water (0.41ml) was added to a stirred solution of Intermediate 8 (0.1g, 0.303mmol) in ethanol (1ml), and the resulting mixture was heated at 50°C. After 1h, the cooled reaction mixture was adjusted to pH3 with 2M hydrochloric acid, and extracted with EtOAc (2 x 6ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give Intermediate 16 (0.072g) as a white solid. LCMS showed $MH^+ = 303$; $T_{RET} = 2.13$min.

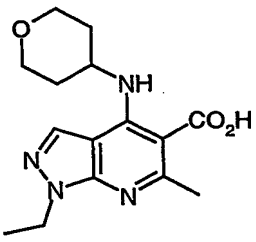
An alternative preparation of Intermediate 16 is as follows:
A solution of sodium hydroxide (0.792g, 19.8mmol) in water (6ml) was added to a stirred solution of Intermediate 8 (1.487g, 4.5mmol) in EtOH (15ml), and the resulting mixture was heated at 50°C. After 1 hour, the cooled reaction mixture was adjusted to pH4 with 2M hydrochloric acid, and extracted with EtOAc (3 x 30ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give Intermediate 16 (1.188g) as a white solid. LCMS showed $MH^+ = 303$; $T_{RET} = 2.12$min.

Intermediate 17: 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



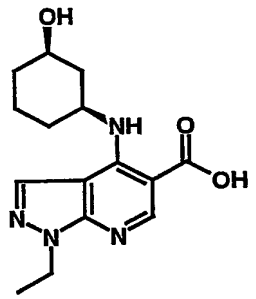
A solution of Intermediate 16 (0.58g, 1.92mmol), hydroxylamine hydrochloride (0.26g, 3.74mmol) and DIPEA (0.65g, 5.03mmol) in MeCN (35ml) was stirred and heated at reflux for 3 hours, then cooled and left at room temperature overnight. Glacial AcOH (1 ml) was added, with stirring. The reaction mixture was concentrated *in vacuo*. EtOAc (10 ml) was added and the resultant suspension was stirred for 30 min. then applied to an SPE cartridge (silica, 20g). The cartridge was eluted with a (250:1) mixture of EtOAc and glacial AcOH, followed by a (500:16:1) mixture of EtOAc, MeOH and glacial AcOH, to give Intermediate 17 (0.327g) as a white solid. LCMS showed $MH^+ = 318$; $T_{RET} = 2.21$min.

Intermediate 18: **1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid**



2M-Sodium hydroxide solution (0.75ml, 1.5mmol) was added to Intermediate 11 (0.248g, 0.75mmol) in EtOH (2ml), and the mixture was heated at reflux for 16 hours. The reaction mixture was concentrated, diluted with water (1ml) and acidified with 2M-hydrochloric acid (0.75ml) to precipitate a solid which was collected by filtration to afford Intermediate 18 (0.168g). LCMS showed $MH^+ = 305$; $T_{RET} = 1.86$min.

Intermediate 19: **1-Ethyl-4-{[(1*SR*,3*RS*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid**



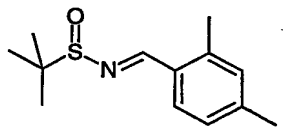
(*cis*-3-hydroxycyclohex-1-ylamino group, racemic)

A solution of Intermediate 12 (0.681g, 2.05mmol) in EtOH (7ml) was treated with a solution of sodium hydroxide (0.362g, 9.05mmol) in water (2.9ml). The resulting mixture was stirred at 50°C. After 3h, the reaction mixture was concentrated *in vacuo* to give a residual oil which was dissolved in water (3ml), then cooled and acidified to pH 3 with 2M hydrochloric acid. After stirring at 0°C for 1h, the resulting precipitate was collected by filtration, washed with cooled water (0.5ml) and dried *in vacuo* to afford Intermediate 19 as a white solid (0.491g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.14$min.

Intermediates 20-86

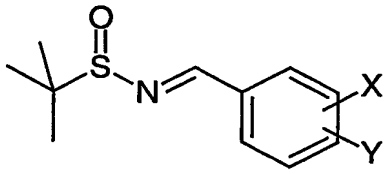
These intermediates were prepared using a modification of the procedure developed by D. A. Cogan, G. Liu and J. Ellman and described in *Tetrahedron*, 1999, *55*, 8883-8904. Compounds are novel unless stated. Compounds containing an alpha substituent on the benzylic carbon (Intermediates 37-86) are enriched in the enantiomer/diastereoisomer which is believed to have the R-stereochemistry at the carbon centre.

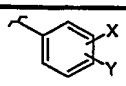
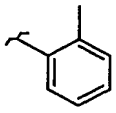
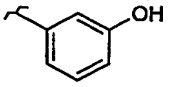
Intermediate 20: N-[(1*E*)-(2,4-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide

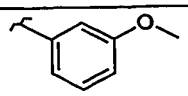
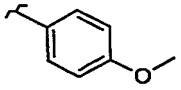
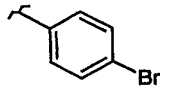
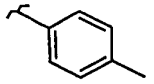
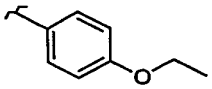
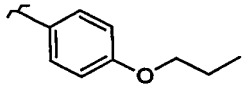
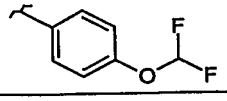
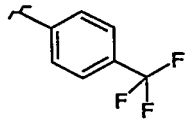
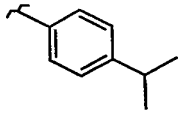
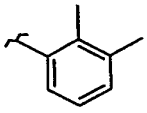
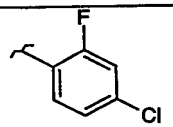
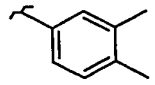
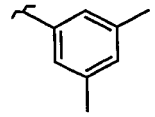
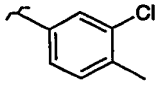


A solution of (S)-tert butyl sulphinamide (0.20g, 1.65mmol) in THF (2ml) was added to 2,4-dimethylbenzaldehyde (0.22g, 1.57mmol). The solution was made up to 10ml with THF. Titanium (IV) ethoxide (0.75g, 3.38mmol) was added and the reaction mixture was heated at 75° for 2 hours. The reaction mixture was cooled and poured onto saturated brine, with vigorous stirring. Celite was added to the resulting suspension, which was filtered and washed with DCM. The organic phase was separated from the aqueous phase by passing through a hydrophobic frit. The DCM was evaporated. The residue was purified on a 50g SPE cartridge, eluting first with a (9:1) mixture of cyclohexane and EtOAc and then with a (4:1) mixture of cyclohexane and EtOAc. Fractions containing the required product were combined and concentrated *in vacuo* to give Intermediate 20 (0.29g) as a white solid. LCMS showed $MH^+ = 238$; $T_{RET} = 3.43$min.

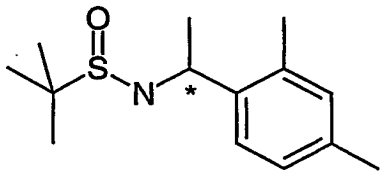
The following intermediates 21-36 were prepared in a similar manner from (S)-tert butyl sulphinamide and the appropriate commercially available aldehyde:



Inter-mediate no.		MH^+ ion	T_{RET} (min)	Reference (if known)
21		224	3.25	
22		226	2.85	

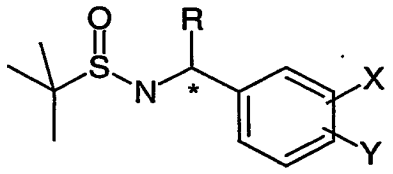
23		240	3.06	
24		240	3.03	Tetrahedron, 1999, **55**, 8883-8904
25		287 & 289	3.36	Tetrahedron Asymm; 2002, **13**, 303-310
26		224	3.2	
27		254	3.32	
28		269	3.31	
29		276	3.27	
30		278	3.46	J. Org. Chem; 2003, **68**, 6894-6898
31		252	3.53	
32		238	3.40	
33		262	3.42	
34		239	3.41	
35		238	3.38	
36		258	3.56	

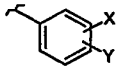
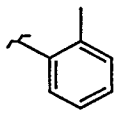
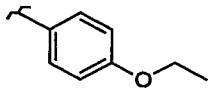
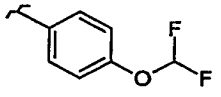
<u>Intermediate 37:</u> **N-[1-(2,4-dimethylphenyl)ethyl]-2-methyl-2-propanesulfinamide**

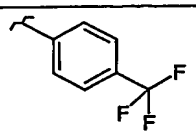
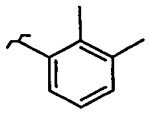
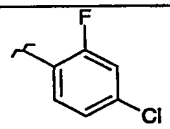
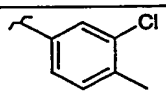
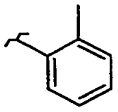
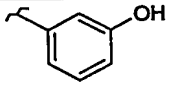
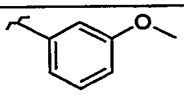
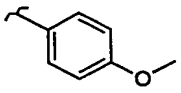
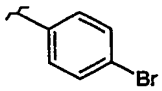
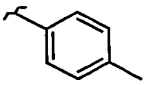
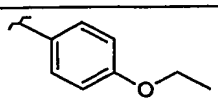
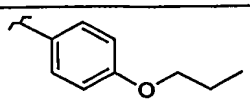
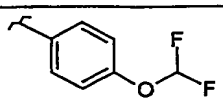
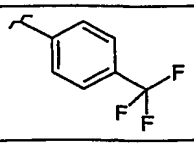


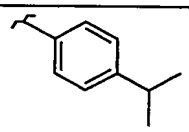
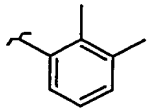
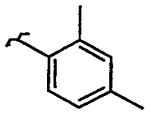
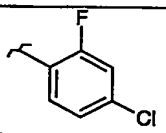
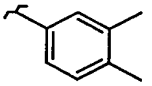
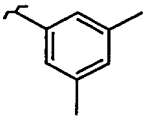
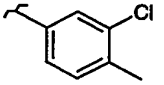
A 3.0 Molar solution of methyl magnesium bromide in Et_2O (2.6ml) was added dropwise, with stirring, to a solution of Intermediate 20 (0.14g, 0.59mmol) in dry THF (5ml) at –10°C. The reaction mixture was stirred at –10°C for 3 hours then gradually warmed to 20°C over 24 hours. The reaction mixture was cooled to 0 °C and treated, dropwise, with saturated ammonium chloride, with vigorous stirring. Once effervescence had ceased more ammonium chloride (5ml) was added, followed by DCM (30ml). The reaction mixture was stirred for 30 min. then the organic phase was filtered through a hydrophobic frit. The DCM was evaporated to leave Intermediate 37 (0.15g) as a white solid (mixture of diastereoisomers). LCMS showed $MH^+ = 254$; $T_{RET} = 3.13$min.

The following Intermediates 38-61 were prepared in a similar manner from Intermediates 20-36, using either a 3.0 Molar solution of methylmagnesium bromide in diethyl ether (R = Me) or a 3.0 Molar solution of ethylmagnesium bromide in diethyl ether (R = Et):

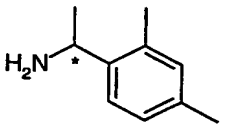


Inter-mediate no.	R		Precursor	MH^+ ion	T_{RET} (min)	Reference (if known)
38	Me		Intermediate 21	240	2.95	
39	Me		Intermediate 27	270	2.97	
40	Me		Intermediate 29	292	3.00	

41	Me		Intermediate 30	294	3.17	
42	Me		Intermediate 32	254	3.10	
43	Me		Intermediate 33	278	3.16	
44	Me		Intermediate 34	274	3.25	
45	Et		Intermediate 21	254	3.10	
46	Et		Intermediate 22	256	2.56 & 2.69	
47	Et		Intermediate 23	270	2.86 & 2.94	
48	Et		Intermediate 24	270	2.86 & 2.93	Tetrahedron, 1999, **55**, 8883-8904
49	Et		Intermediate 25	317 & 319	3.17	
50	Et		Intermediate 26	254	3.14	
51	Et		Intermediate 27	284	3.16	
52	Et		Intermediate 28	298	3.24 & 3.28	
53	Et		Intermediate 29	306	3.18	
54	Et		Intermediate 30	308	3.30	

55	Et		Intermediate 31	282	3.43	
56	Et		Intermediate 32	268	3.24	
57	Et		Intermediate 20	268	3.28	
58	Et		Intermediate 33	292	3.30	
59	Et		Intermediate 34	268	3.26 & 3.31	
60	Et		Intermediate 35	268	3.28 & 3.33	
61	Et		Intermediate 36	288	3.3	

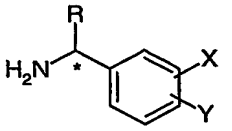
Intermediate 62: **1-(2,4-dimethylphenyl)ethyl]amine hydrochloride** (Racemate: Tim Tec Building Blocks B)



(Mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry)

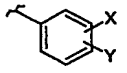
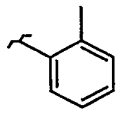
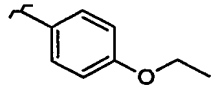
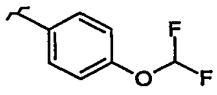
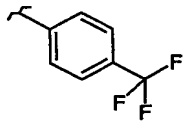
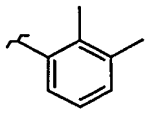
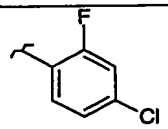
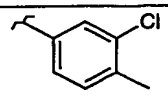
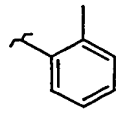
A solution of Intermediate 37 (151mg, 0.60mmol) in a mixture of 4.0M HCL in dioxan (1ml) and MeOH (1ml) was left to stand for 1 hour. The solvents were evaporated. The residue was triturated in Et_2O containing a few drops of MeOH to give a solid suspension. The solid was filtered off and dried to give Intermediate 62 (76mg) as a white solid. LCMS showed $MH^+ = 150$; $T_{RET} = 1.84$min.

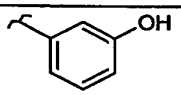
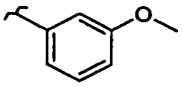
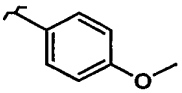
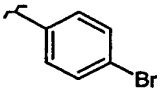
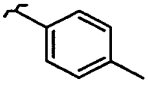
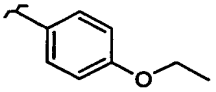
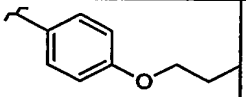
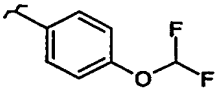
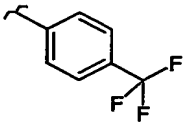
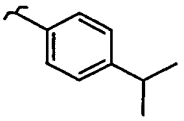
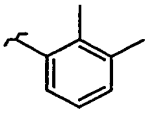
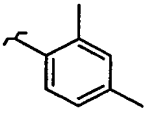
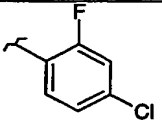
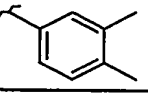
The following Intermediates 63-86 were prepared in a similar manner from Intermediates 38-61:

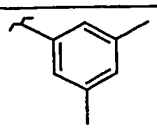
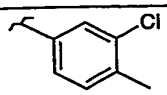


.HCl

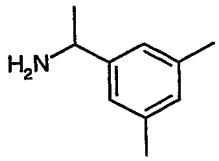
(Mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry)

Inter-mediate no.	**R**		**Precursor**	**MH^+ ion**	**T_{RET} (min)**	**Reference or Commercial Supplier (if known):** reference may be made to the racemate and/or the (R)-enantiomer
63	Me		Intermediate 38	136	1.33	ACB Blocks Product List
64	Me		Intermediate 39	[MH-16]=149	1.77	ACB Blocks Product List
65	Me		Intermediate 40	188	1.65	Braz. Pedido Pl; 1989, BR8804596
66	Me		Intermediate 41	190	1.88	ACB Blocks Product List
67	Me		Intermediate 42	150	1.81	Agr. And Biol. Chem; 1973, **37**, 981-988
68	Me		Intermediate 43	174	1.60	
69	Me		Intermediate 44	169	1.95	Eur. Patent Application EP191496 A2 (1986)
70	Et		Intermediate 45	150	1.81	Tetrahedron Lett; 1986, **27**, 1331-1334

71	Et		Intermediate 46	152	1.16	
72	Et		Intermediate 47	166	1.69	World Patent WO2002083624 (2002)
73	Et		Intermediate 48	166	1.67	Tetrahedron Lett; 1998, **39**, 3559-3562
74	Et		Intermediate 49	214 & 216	1.9	Synthesis, 1999, 930-934
75	Et		Intermediate 50	150	1.78	Tetrahedron Asymm; 1999, **10**, 1579-1588
76	Et		Intermediate 51	[M-16]=163	1.96	
77	Et		Intermediate 52	194	2.07	
78	Et		Intermediate 53	202	1.95	Pesticide Sci; 1998, **54**, 223
79	Et		Intermediate 54	204	2.12	World Patent WO2002051809 (2002)
80	Et		Intermediate 55	178	2.1	
81	Et		Intermediate 56	164	2.01	
82	Et		Intermediate 57	164	2.04	
83	Et		Intermediate 58	188	1.93	
84	Et		Intermediate	164	2.00	World Patent WO200208362

			59			4 (2002)
85	Et		Intermediate 60	164	2.04	World Patent WO2002083624 (2002)
86	Et		Intermediate 61	185	2.13	

Intermediate 87: [1-(3,5-dimethylphenyl)ethyl]amine hydrochloride (Jpn. Kokai Tokkyo Koho JP 62294669 (1987))

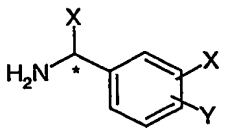


.HCl

(Racemic)

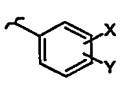
A mixture of (3,5-dimethyl)acetophenone (0.95g, 7.0mmol), formamide (1.4ml, 1.58g, 35.0mmol) and formic acid (0.81ml, 0.97g, 21.0 mmol) was heated at 160^0 for 18 hours. The reaction mixture was cooled and partitioned between EtOAc and water. The organic phase was separated, washed with potassium carbonate solution and sodium chloride solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was treated with 2M hydrochloric acid (10ml) and the resultant mixture was heated at reflux for 18 hours, cooled to room temperature and washed with DCM (2x10ml). The aqueous solution was concentrated *in vacuo* to leave Intermediate 87 (0.42g) as a white solid. LCMS showed $MH^+ = 150$; $T_{RET} = 1.88$min.

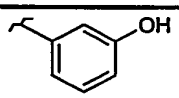
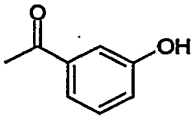
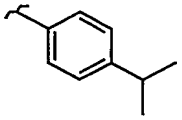
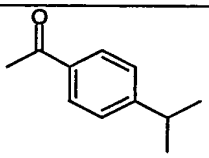
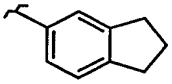
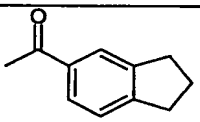
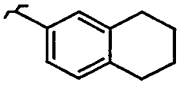
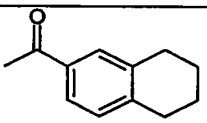
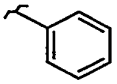
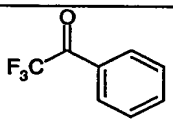
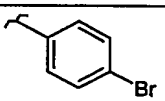
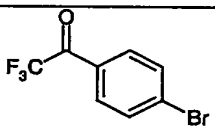
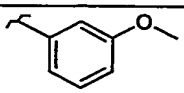
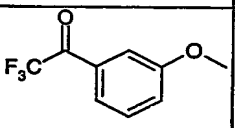
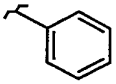
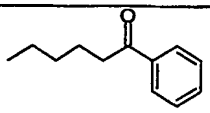
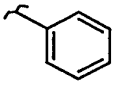
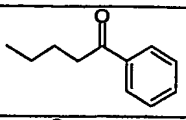
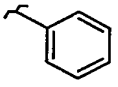
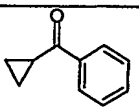
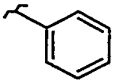
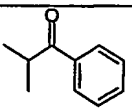
The following racemic Intermediates 88-99 were made in a similar manner from the appropriate acetophenone (commercially available unless stated):

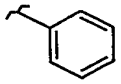
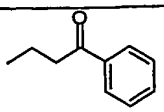


.HCl

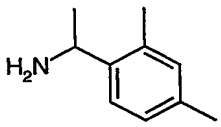
(Racemic)

Inter-mediate no.	**X**		**Precursor**	**MH^+ ion**	**T_{RET} (min)**	**Reference or Commercial Supplier (if known):** reference may be made to the racemate

						and/or the (R)-enantiomer
88	Me			138	2.29	Tetrahedron, 1977, **33**, 489
89	Me			164	2.04	Tim Tec Building Blocks B
90	Me			162	1.91	Jpn. Kokai Tokkyo Koho JP 07101939 A2 (1995)
91	Me			176	2.13	Jpn. Kokai Tokkyo Koho JP 07101939 A2 (1995)
92	CF_3			176	1.55	Microchemistry Building Blocks
93	CF_3			255	2.53	Angew. Chem. Int. Ed; 2001, **40**, 589-590
94	CF_3			206	1.94	
95	-$(CH_2)_4CH_3$			178	2.24	J. Combinatorial Chem; 2001, **3**, 71-77
96	-$(CH_2)_3CH_3$			164	2.00	Civentichem.
97				148	0.90	ACB Blocks
98	-$CH(CH_3)_2$			150	1.71	Civentichem.

99	- $(CH_2)_2CH_3$			150	1.79	Heterocyclic Compounds Catalog

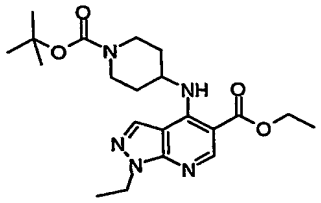
Intermediates 100-101: [1-(2,4-dimethylphenyl)ethyl]amine trifluoroacetate



[(R)- and (S)- enantiomers]

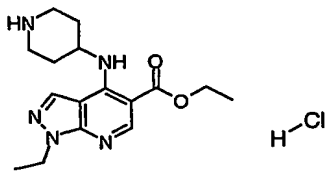
Intermediate 62 (0.40g) was resolved by preparative chiral column chromatography, using a 2-inch x 20cm Chiracel OJ column with a (2:98) mixture of heptane and ethanol, containing 0.1% trifluoroacetic acid, as the eluent. Intermediate 100 (first enantiomer to elute: 0.21g) and Intermediate 101 (second enantiomer to elute: 0.12g) were separated on the column. LCMS showed MH^+ = 150; T_{RET} = 1.76min. for both enantiomers.

<u>Intermediate 102</u>: Ethyl 4-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



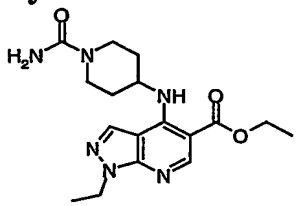
A solution of Intermediate 1 (2.3g) in acetonitrile (50ml) was treated with solid 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate (2g) and DIPEA (8.6ml). The reaction mixture was heated at 90°C for 16h. The solvents were removed under reduced pressure and the residue was partitioned between DCM (100ml) and water (75ml). The organic fraction was collected through a hydrophobic frit and the solvents were removed under reduced pressure to yield Intermediate 102 as a white solid (3.9g). LCMS showed MH^+ = 418; T_{RET} = 3.35min.

<u>Intermediate 103</u>: Ethyl 1-ethyl-4-(4-piperidinylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate hydrochloride



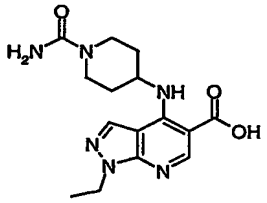
Intermediate 102 (3.9g) was treated with 4.0M hydrogen chloride in 1, 4-dioxane (30ml) and the reaction mixture was stirred at 22°C for 1h. The solvents were removed to give Intermediate 103 as a white solid (3.9g). LCMS showed $MH^+ = 318$; $T_{RET} = 2.21$min.

Intermediate 104: Ethyl 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



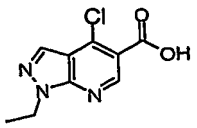
A suspension of intermediate 103 (3.9g) in THF (100ml) was treated with trimethylsilyl isocyanate (1.99ml) followed by DIPEA (2.6ml) and the solution was stirred at 22°C for 2h. The volatile solvents were removed under reduced pressure and the residue was partitioned between DCM (50ml) and water (25ml). The organic layer was collected. The aqueous phase was re-extracted with DCM (50ml). The organic layers were combined, separated from water by passing through a hydrophobic frit and concentrated under reduced pressure to yield Intermediate 104 as a white solid (3.9g). LCMS showed $MH^+ = 361$; $T_{RET} = 2.45$min.

Intermediate 105: 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of intermediate 104 (3.9g) in ethanol (50ml) was treated with a solution of sodium hydroxide (1.77g) in water (20ml) and the reaction mixture was heated at 80°C for 16h. LCMS indicated that partial hydrolysis of the urea portion had occurred. The solvents were removed and the residue was dissolved in water (5ml), the pH was adjusted to 3 (2M HCl) and the resultant white precipitate was collected by filtration and dried. This precipitate was dissolved in ethanol. The solution was treated with trimethylsilyl isocyanate (3ml) and DIPEA (10ml) and then stirred at 22°C for 16h. The solvents were removed and the residue was dissolved in water (5ml), the pH was adjusted to 3 (2M HCl) and the resultant white precipitate was collected by filtration and dried to give Intermediate 105 as a white solid (2.66g). LCMS showed $MH^+ = 333$; $T_{RET} = 2.00$min.

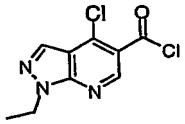
Intermediate 106: 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A solution of Intermediate 1 (20g) in 1,4-dioxane (100ml) was treated with a solution of potassium hydroxide (18g) in water (30ml) and the reaction mixture was stirred at 22°C for 24h. The solvent was evaporated and the residue was acidified to pH 3 (2M HCl). The resultant white precipitate was collected by filtration and dried to give Intermediate 106 as a white solid (16.9g). LCMS showed $MH^+ = 226$; $T_{RET} = 2.45$min.

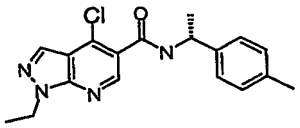
Alternative synthesis: A solution of Intermediate 1 (3.5g) in dioxane (28ml) was treated with potassium hydroxide (6.3g) as a solution in water (20ml). The mixture was stirred for 2h, then concentrated in vacuo, acidified to pH 3 with 2M aqueous hydrochloric acid and extracted with ethyl acetate. The layers were separated, the organic layer dried over sodium sulphate, then concentrated in vacuo to afford Intermediate 106 as a white solid (2.4g). LCMS showed $MH^+ = 226$; $T_{RET} = 2.62$min.

Intermediate 107: 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride



A solution of intermediate 106 (17.8g) in thionyl chloride (100ml) was heated under reflux for 3.5h. The solution was cooled to room temperature. The thionyl chloride was removed *in vacuo* and any remaining thionyl chloride was removed by azeotropic distillation with toluene (30ml) to give Intermediate 107 as a beige solid (16.8g). LCMS (MeOH solution) showed $MH^+ = 240$ (Methyl ester); $T_{RET} = 2.88$min.

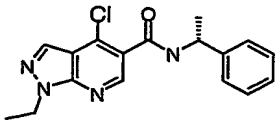
Intermediate 108: 4-chloro-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



A solution of intermediate 107 (2.0g) in THF (20ml) was treated with (R)-(+)-1-(methylphenyl) ethylamine (1.11g) and DIPEA (1.06g). The reaction mixture was stirred at 22°C for 24h. The solvent was evaporated and the residue was dissolved in DCM (50ml). The solution was washed with 5% citric acid solution (50ml) and 0.5M sodium bicarbonate solution (50ml), dried (Na_2SO_4), filtered and concentrated to give Intermediate 108 as a white solid (1.61g). LCMS showed $MH^+ = 343$; $T_{RET} = 3.22$min.

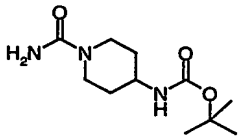
The following Intermediate 109 was prepared in an analogous manner:

Intermediate 109: 4-chloro-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



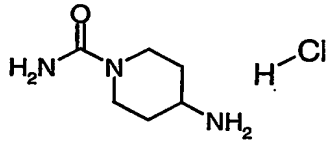
LCMS showed $MH^+ = 329$; $T_{RET} = 3.0$min.

Intermediate 110: 1,1-dimethylethyl [1-(aminocarbonyl)-4-piperidinyl]carbamate



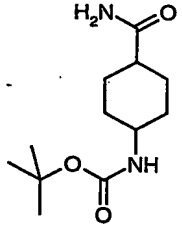
A solution of 1,1-dimethylethyl 4-piperidinylcarbamate (0.35g) in DCM (10ml) was treated with trimethylsilyl isocyanate (1.1ml). The reaction mixture was stirred at 22°C for 72h. The mixture was diluted with saturated $NaHCO_3$ (20ml). The organic phase was collected through a hydrophobic frit and evaporated to give Intermediate 110 as a white foam (0.29g). ^{1}H NMR (400MHz in $CDCl_3$, 27°C, δ ppm) 4.45 (br. s, 3H). 3.90 (d, 2H), 3.65 (br. m, 1H), 2.9-3.0 (dt, 2H), 1.95-2.0 (br. dd, 2H), 1.45 (s, 9H), 1.3-1.4 (dq, 2H).

Intermediate 111: 4-amino-1-piperidinecarboxamide hydrochloride



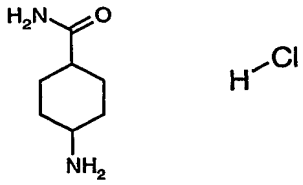
A solution of intermediate 110 (0.29g) in 4.0M hydrogen chloride in 1, 4-dioxane (5ml) was stirred at 22°C for 4h. The solvent was evaporated to give Intermediate 111 as a white foam (0.27g). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δ ppm) 8.1 (br. s, 2H), 3.95 (d, 2H), 3.15 (m, 1H), 2.7 (dt, 2H), 1.85 (dd, 2H), 1.35 (m, 2H).

Intermediate 112: 1,1-dimethylethyl [4-(aminocarbonyl)cyclohexyl]carbamate



A solution of 4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid (ex. Fluka, 1g) in DMF (30ml) was treated with HATU (1.72g) and DIPEA (5.4ml). The reaction mixture was stirred at 22°C for 10 min. A 0.5M solution of ammonia in 1,4-dioxane (40ml) was added and the reaction mixture was stirred at 22°C for 72h. The solvents were evaporated and the residue was purified by loading the crude mixture onto a 50g aminopropyl SPE cartridge and eluting with ethyl acetate (100ml), then methanol (100ml). Intermediate 112 was isolated by evaporation of the methanol fraction as a yellow oil (0.99g). LCMS showed $MH^+ = 242$; $T_{RET} = 2.2$min.

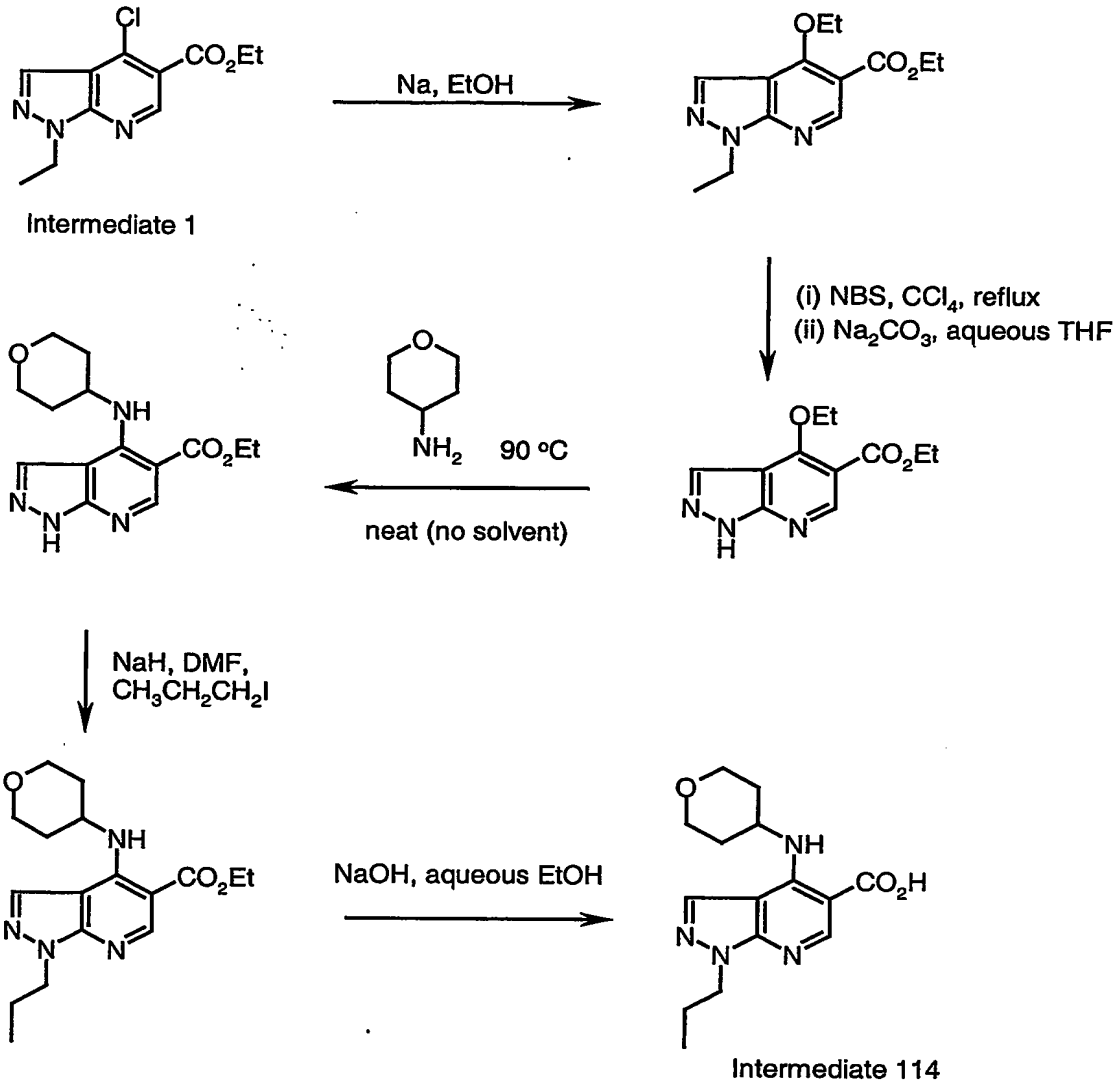
Intermediate 113: 4-aminocyclohexanecarboxamide hydrochloride



4.0M hydrogen chloride in 1,4-dioxane (14ml) was added to intermediate 112 (0.99g) and the reaction mixture was stirred at 22°C for 30min. The solvent was evaporated to give Intermediate 113 as a yellow gum (1.03g). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 7.9 (br. S, 2H), 3.9 (br. S, 2H), 3.10 (m, 1H), 1.92 (m, 2H), 1.68 (m, 4H), 1.50 (m, 2H).

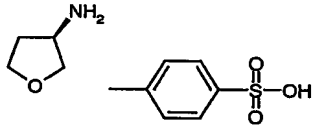
Intermediate 114:

Intermediate 114 was synthesised according to the following reaction scheme:

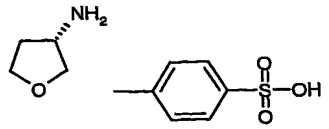


Intermediate 114

Intermediate 115: (R)-(+)-3-Amino tetrahydrofuran 4-toluenesulphonate
Commercially available from Fluka Chemie AG, Germany (CAS 111769-27-8)

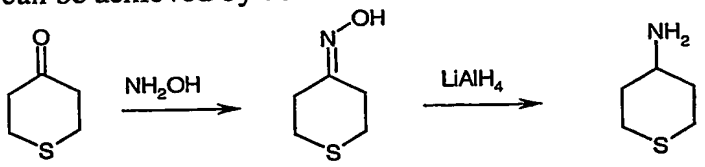


Intermediate 116: (S)-(-)-3-Amino tetrahydrofuran 4-toluenesulphonate
Commercially available from E. Merck, Germany; or from E. Merck (Merck Ltd), Hunter Boulevard, Magna Park, Lutterworth, Leicestershire LE17 4XN, United Kingdom (CAS 104530-80-5)



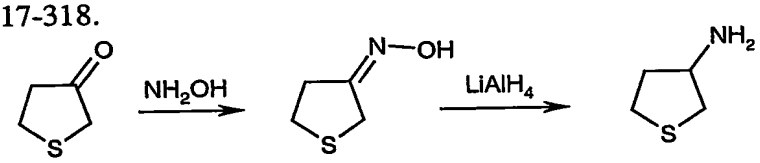
Intermediate 117: Tetrahydro-2H-thiopyran-4-amine

Prepared from commercially available tetrahydrothiopyran-4-one as described by Subramanian et. al., *J. Org. Chem.*, 1981, 46, 4376-4383. Subsequent preparation of the hydrochloride salt can be achieved by conventional means.



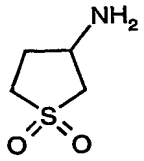
Intermediate 118: Tetrahydro-3-thiopheneamine

Prepared in an analogous manner to Intermediate 117 from commercially available tetrahydrothiophene-4-one. The oxime formation is described by Grigg et.al., *Tetrahedron*, 1991, 47, 4477-4494 and the oxime reduction by Unterhalt et. al., *Arch. Pharm.*, 1990, 317-318.



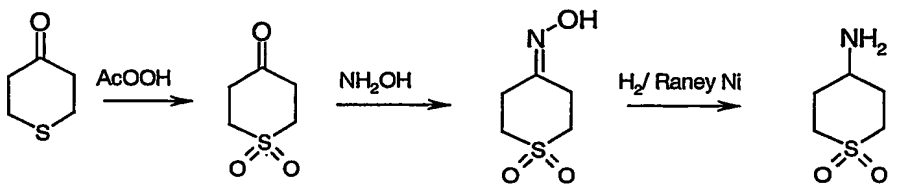
Intermediate 119: Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride

Commercially available from Sigma Aldrich Library of Rare Chemicals (SALOR) (CAS-6338-70-1). Preparation of the hydrochloride salt of the amine can be achieved by conventional means.

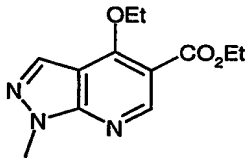


Intermediate 120: Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride

Prepared in an analogous manner to Intermediate 117 from commercially available tetrahydrothiophene-4-one. Oxidation to 1,1-dioxo-tetrahydro-1λ^6-thiopyran-4-one is described by Rule et. al., in *J. Org. Chem.*, 1995, 60, 1665-1673. Oxime formation is described by Truce et.al., in *J. Org. Chem.*, 1957, 617, 620 and oxime reduction by Barkenbus et. al., *J. Am. Chem. Soc.*, 1955, 77, 3866. Subsequent preparation of the hydrochloride salt of the amine can be achieved by conventional means.

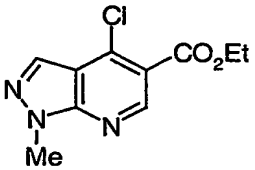


Intermediate 121: Ethyl 1-methyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



A mixture of Intermediate 1A (0.47g) and anhydrous potassium carbonate (0.83g) (previously dried by heating at 100°C) in anhydrous dimethylformamide (DMF) (4ml) was treated with iodomethane (0.26ml) and stirred vigorously for 3h. The mixture was then filtered and the filtrate concentrated in vacuo to afford a residual oil, which was partitioned between dichloromethane (DCM) (25ml) and water (25ml). The layers were separated and the aqueous phase was extracted with further DCM (2x25ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to an orange solid which was applied to an SPE cartridge (silica, 20g). The cartridge was eluted sequentially with EtOAc : petrol (1:4, 1:2 and 1:1), then chloroform : methanol (49:1, 19:1 and 9:1). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 121 (0.165g). LCMS showed MH^+= 250; T_{RET} = 2.59 min.

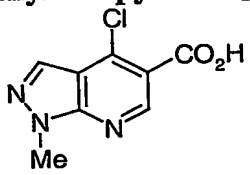
Intermediate 122: Ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



A mixture of 5-amino-1-methyl pyrazole (4.0g) and diethylethoxymethylene malonate (9.16ml) was heated at 150°C under Dean Stark conditions for 5h. Phosphorous oxychloride (55ml) was carefully added to the mixture and the resulting solution heated at 130°C under reflux for 18h. The mixture was concentrated in vacuo, then the residual oil cooled in an ice bath and treated carefully with water (100ml)(caution: exotherm). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous sodium sulphate and concentrated in vacuo. The residual solid

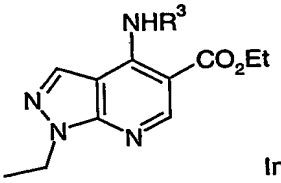
was purified by Biotage chromatography (silica, 90g), eluting with Et_20 : petrol (1:3). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 122 (4.82g). LCMS showed $MH^+ = 240$; $T_{RET} = 2.98$min

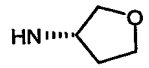
Intermediate 123: 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 122 (4.0g) in dioxane (30ml) was treated with potassium hydroxide (7.54g) as a solution in water (20ml). The mixture was stirred for 16h, then diluted with water (150ml) and acidified to pH 3 with 5M aqueous hydrochloric acid. The mixture was stirred in an ice bath for 15min, then collected by filtration, washed with ice-cold water and dried in vacuo over phosphorous pentoxide to afford Intermediate 123 as a white solid (2.83g). LCMS showed $MH^+ = 212$; $T_{RET} = 2.26$min.

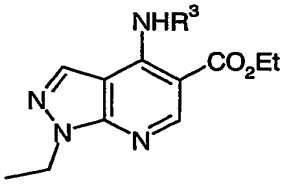
Intermediate 124: Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

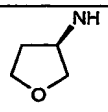
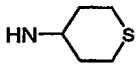
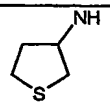
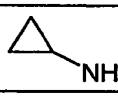


Intermediate 124 NHR^3 = 

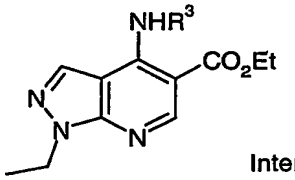
Intermediate 1 (0.05g) and (S)-(-)-3-aminotetrahydrofuran 4-toluenesulphonate (Intermediate 116) (0.052g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:16 then, 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 124 (0.052g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.70$min.

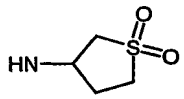
Similarly prepared were the following:



	NHR^3	Amine Reagent	MH$^+$ ion	T_{RET}(min)
Intermediate 125		(R)-(+)-3-Aminotetrahydrofuran 4-toluenesulphonate (Intermediate 115)	305	2.73
Intermediate 126		Intermediate 117	335	3.21
Intermediate 127		Intermediate 118	321	3.10
Intermediate 128		Cyclopropylamine	275	2.98

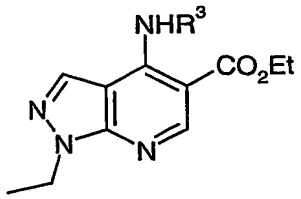
<u>Intermediate 129:</u> Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

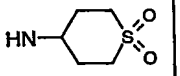


Intermediate 129 NHR^3 = 

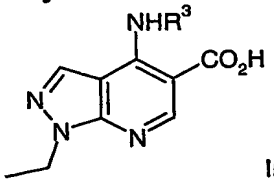
Intermediate 1 (0.05g) and Intermediate 119 (0.027g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:8 then 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 129 (0.045g) as a mixture of enantiomers. LCMS showed MH$^+$ = 353; T_{RET} = 2.60min.

Similarly prepared was the following:



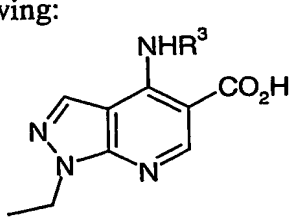
	NHR3	Amine Reagent	MH+ ion	TRET(min)
Intermediate 130		Intermediate 120	367	2.64

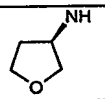
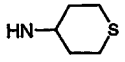
Intermediate 131: 1-Ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

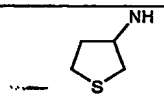
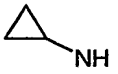
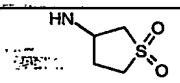
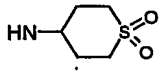


A solution of Intermediate 124 (0.037g) in ethanol : water (95:5, 3ml) was treated with sodium hydroxide (0.019g). The mixture was heated at 50°C for 16h, then concentrated in vacuo. The residue was dissolved in water (1.5ml) and acidified to pH 4 with acetic acid. The resultant white solid precipitate was removed by filtration and dried under vacuum. The filtrate was extracted with ethyl acetate and the organic layer collected and concentrated in vacuo to afford a further portion of white solid. The two solids were combined to afford Intermediate 131 (0.033g). LCMS showed MH^+ = 277; T_{RET} = 2.05 min.

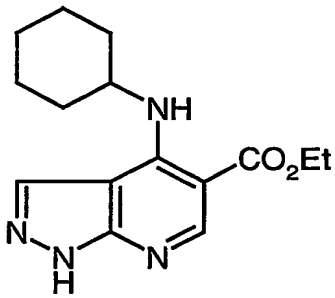
Similarly prepared were the following:



	NHR3	Starting material	MH+ ion	TRET(min)
Intermediate 132		Intermediate 125	277	2.05
Intermediate 133		Intermediate 126	307	2.40

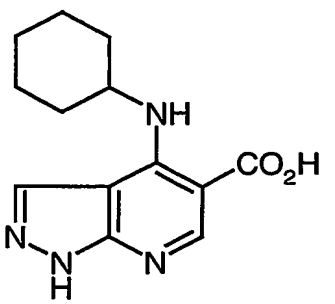
Intermediate 134		Intermediate 127	293	2.59
Intermediate 135		Intermediate 128	247	2.24
Intermediate 136		Intermediate 129	325	2.05
Intermediate 137		Intermediate 130	339	2.05

<u>Intermediate 148</u>: Ethyl 4-(cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



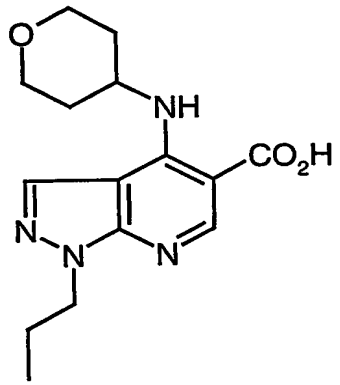
Intermediate 1A (0.69g) was suspended in cyclohexylamine (1.01ml), and the mixture was heated at 90 °C for 3h. The residual mixture was allowed to cool to room temperature and partitioned between chloroform (25ml) and water (25ml). The phases were separated and the organic phase was evaporated to dryness. The residue was triturated with Et_2O (25ml) and the insoluble solid was collected and dried to afford Intermediate 148 as a beige solid (0.58g). LCMS showed MH^+=289; T_{RET} = 2.91min.

<u>Intermediate 149</u>: 4-(Cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



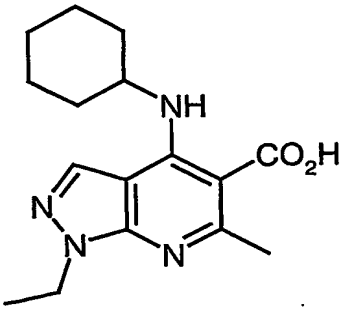
2M-Sodium hydroxide solution (0.5ml) was added to a stirred suspension of Intermediate 48 (0.2g) in dioxan (4ml) and water (0.5ml). After stirring overnight at room temperature, the reaction mixture was heated at 40 °C for 8h. A further quantity of 2M-sodium hydroxide solution (1.5ml) was added, and the reaction mixture was heated at 40 °C for 48h. The reaction solution was concentrated, diluted with water (10ml) and acidified with glacial acetic acid. The resulting precipitate was collected by filtration, washed with water and dried to give Intermediate 149 (0.18g). LCMS showed $MH^+ = 261$; $T_{RET} =$ 2.09min.

Intermediate 150: 1-n-Propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



2M-Sodium hydroxide solution (0.7ml) was added to a stirred suspension of the corresponding ethyl ester (0.23g) in ethanol (5ml) and water (1.5ml). After stirring overnight at room temperature, a further quantity of 2M-sodium hydroxide solution (0.7ml) was added, and the reaction mixture was heated at 43 °C for 2.5h. The reaction solution was concentrated, diluted with water (5ml) and acidified with 2M-hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried to give Intermediate 150 as a white solid (0.14g). LCMS showed $MH^+ = 305$; $T_{RET} =$ 2.42min.

Intermediate 152: 4-(Cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid

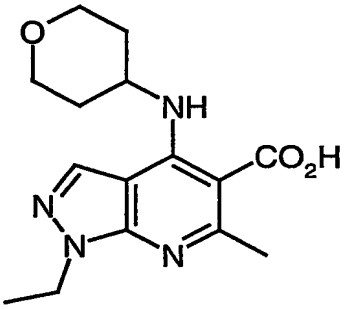


2M-Sodium hydroxide solution (0.39ml, 0.78mmol) was added to the corresponding ethyl ester (0.128g, 0.39mmol) in ethanol (1.5ml), and the mixture was heated at 50 °C

for 16 hours. The reaction mixture was concentrated, and the resulting aqueous solution was neutralised with 2M-hydrochloric acid to precipitate a solid which was collected by filtration. The filtrate was applied to an OASIS ® hydrophilic-lipophilic balance (HLB) Extraction cartridge * (1g) which was eluted with water followed by methanol. Evaporation of the methanol fraction gave a solid which was combined with the initial precipitated solid to afford Intermediate 152 (0.083g) as a white solid, presumed to be the carboxylic acid.

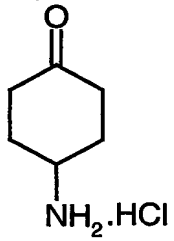
* OASIS ® HLB Extraction cartridges are available from Waters Corporation, 34 Maple Street, Milford, MA 01757, USA. The cartridges include a column containing a copolymer sorbent having a HLB such that when an aqueous solution is eluted through the column, the solute is absorbed or adsorbed into or onto the sorbent, and such that when organic solvent (e.g. methanol) is eluted the solute is released as an organic (e.g. methanol) solution. This is a way to separate the solute from aqueous solvent.

Intermediate 153: **1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid**



2M-Sodium hydroxide solution (0.75ml, 1.5mmol) was added to Intermediate 11 (0.248g, 0.75mmol) in ethanol (2ml), and the mixture was heated at reflux for 16 hours. The reaction mixture was concentrated, diluted with water (1ml) and acidified with 2M-hydrochloric acid (0.75ml) to precipitate a solid which was collected by filtration to afford Intermediate 153 (0.168g). LCMS showed $MH^+ = 305$; $T_{RET} = 1.86$min.

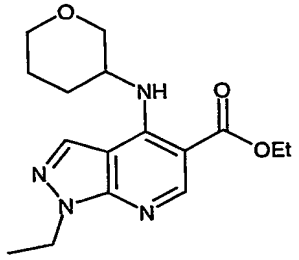
Intermediate 154: **4-Aminocyclohexanone hydrochloride**



A solution of hydrogen chloride in dioxan (0.5ml, 2.0mmol, 4M) was added to a stirred solution of *tert*-butyl 4-oxocyclohexylcarbamate (0.043g, 0.20mmol, commercially available from Astatech Inc., Philadelphia, USA) in dioxan (0.5ml) and the mixture was stirred at room temperature. After 1h, the reaction mixture was evaporated to give Intermediate 154 as a cream solid (34mg). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm)

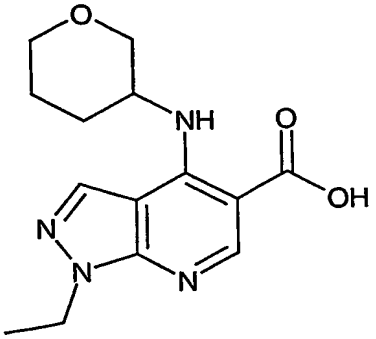
8.09 (br. s, 3H), 3.51 (tt, 11, 3.5Hz, 1H), 2.45 (m, 2H, partially obscured), 2.29 (m, 2H), 2.16 (m, 2H), 1.76 (m, 2H).

Intermediate 158: Ethyl 1-ethyl-4-(tetrahydro-2*H*-pyran-3-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



Intermediate 1 (0.76g, 3.0mmol)) was dissolved in acetonitrile (10ml). Tetrahydro-2*H*-pyran-3-amine hydrochloride (0.5g, 3.6mmol, *Anales De Quimica*, 1988, **84**, 148) and *N,N*-diisopropylethylamine (3.14ml, 18.0mmol) were added and the mixture was stirred at 85°C for 24h. After 24h a further portion of tetrahydro-2*H*-pyran-3-amine hydrochloride (0.14g, 1.02mmol) was added and stirring was continued at 85°C. After a further 8h, the mixture was concentrated *in vacuo*. The residue was partitioned between DCM (20ml) and water (12ml). The layers were separated and the aqueous layer was extracted with further DCM (12ml). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to give a brown solid which was purified on a SPE cartridge (silica, 20g) eluting with a gradient of ethyl acetate:cyclohexane (1:16, 1:8, 1:4, 1:2, 1:1, 1:0). Fractions containing the desired material were combined and evaporated to afford Intermediate 158 (0.89g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.92$ min.

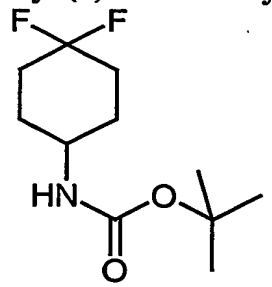
Intermediate 159: 1-Ethyl-4-(tetrahydro-2H-pyran-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 158 (0.89g, 2.79mmol) in ethanol (16.7ml) was treated with sodium hydroxide (0.47g, 11.7mmol) as a solution in water (3.1ml). The mixture was stirred at 50 °C. After 12h, the reaction mixture was concentrated *in vacuo* to give a residual oil which was dissolved in water (16ml), then cooled and acidified to pH 3 with

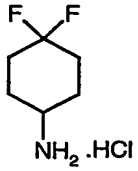
2M hydrochloric acid. After stirring at 0°C for 30min, the resulting precipitate was collected by filtration, washed with cooled water (2ml) and dried in vacuo to afford Intermediate 159 as a white solid (0.73g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.19$min.

Intermediate 162: 1,1-Dimethylethyl (4,4-difluorocyclohexyl)carbamate



(Diethylamino)sulphur trifluoride (DAST), (0.06ml, 0.47mmol), was added to a stirred solution of 1,1-dimethylethyl(4-oxocyclohexyl)carbamate, (250mg, 1.17mmol, commercially available from AstaTech Inc., Philadelphia, USA) in anhydrous dichloromethane (5ml) and the mixture was stirred under nitrogen at 20°C. After 22h, the reaction mixture was cooled to 0°C, treated with saturated sodium hydrogen carbonate solution (4ml), and then allowed to warm to ambient temperature. The phases were separated by passage through a hydrophobic frit and the aqueous phase was further extracted with DCM (5ml). The combined organic phases were concentrated in vacuo to give an orange solid (369mg) which was further purified by chromatography using a SPE cartridge (silica, 10g), eluting with DCM to afford Intermediate 162 (140mg) containing 20% of **1,1-dimethylethyl (4-fluoro-3-cyclohexen-1-yl)carbamate.** ^{1}H NMR (400MHz in $CDCl_3$, 27°C, δppm)
Minor component: δ5.11 (dm, 16Hz, 1H), 4.56 (br, 1H), 3.80 (br, 1H) 2.45-1.45 (m's, 6H excess), 1.43 (s, 9H). Major component: δ4.43 (br, 1H), 3.58 (br, 1H), 2.45-1.45 (m's, 8H excess), 1.45 (s, 9H).

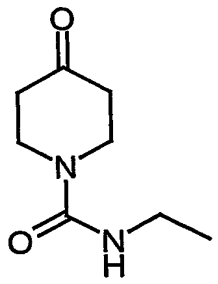
Intermediate 163: (4,4-Difluorocyclohexyl)amine hydrochloride



A solution of hydrogen chloride in dioxane (4M, 1.6ml) was added at 20°C to a stirred solution of Intermediate 62 (140mg, 0.6mmol), in dioxane (1.6ml). After 3h, the reaction mixture was concentrated in vacuo to afford intermediate 163 (96.5mg) containing **4-fluoro-3-cyclohexen-1-amine.** ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) Minor component: δ8.22 (br, 3H excess), 5.18 (dm, 16Hz, 1H), 3.28-3.13 (m, 1H excess), 2.41-

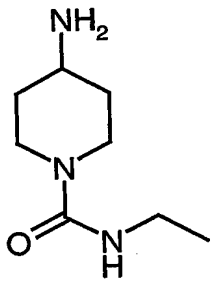
1.53 (m's, 6H excess). Major component: δ8.22 (br, 3H excess), 3.28-3.13 (m, 1H excess), 2.41-1.53 (m's, 8H excess). Impurities are also present.

Intermediate 168: ***N*-Ethyl-4-oxo-1-piperidinecarboxamide**



A solution of ethyl isocyanate (2.31g, 32.5mmol) in DCM (40ml) was added, dropwise over 15min, to a vigorously stirred solution of 4-piperidone monohydrate hydrochloride (5.0g, 32.5mmol, commercially available from Aldrich) and sodium hydrogen carbonate (8.2g, 97.5mmol) in water (60ml) at 0°C. The reaction mixture was stirred at room temperature for 20h. Sodium chloride (7.0g) was added to the reaction mixture and the organic phase was separated. The aqueous phase was extracted with further DCM (3 x 75ml). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give a white solid (4.0g). Recrystallisation from ethyl acetate: cyclohexane (10:1) afforded Intermediate 168 as a white solid (2.3g).
TLC (silica) gave $R_f = 0.24$ (ethyl acetate). Anal. Found: C, 56.7; H, 8.3; N, 16.35. $C_8H_{14}N_2O_2$ requires C, 56.5; H, 8.3; N, 16.5.

Intermediate 169: **4-Amino-*N*-ethyl-1-piperidinecarboxamide**



A solution of Intermediate 168 (1.5g, 8.8mmol) and benzylamine (1.04g, 9.7mmol) in absolute ethanol (60ml) was hydrogenated over pre-reduced 10% palladium on charcoal catalyst (0.6g) in ethanol (20ml) until the uptake of hydrogen had ceased (22h). The reaction mixture was filtered through filter agent (Celite), and then through silica gel (100ml) eluting with ethanol:0.88-ammonia (100:1) to give a black oil. The oil was dissolved in ethanol (30ml) and treated with a solution of hydrogen chloride in ethanol (3M) until the solution was acidic. The solvent was evaporated and the residue was triturated with ethanol to afford Intermediate 169 as a white solid (1.09g).
TLC (silica) gave $R_f = 0.73$ (ethyl acetate:methanol, 10:1). Anal. Found: C, 45.9; H, 8.4; N, 19.8. $C_8H_{18}ClN_3O$ requires C, 46.3; H, 8.7; N, 20.2.

Table of Examples

Example Number	Name
1	1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
2	1-ethyl-*N*-(1-methyl-1-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
3	1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4	*N*-(diphenylmethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
5	1-ethyl-*N*-[1-(3-pyridinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
6	1-ethyl-*N*-[(1*S*)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
7	1-ethyl-*N*-[(1*S*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
8	1-ethyl-*N*-[(1*R*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
9	1-ethyl-*N*-[1-methyl-1-(4-pyridinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
10	1-ethyl-*N*-[(1*R*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
11	*N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
12	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
13	1-ethyl-*N*-(3-hydroxy-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
14	1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
15	*N*-[2-(dimethylamino)-1-phenylethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
16	1-ethyl-*N*-[1-phenyl-2-(1-pyrrolidinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
17	1-ethyl-*N*-[1-(hydroxymethyl)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
18	1-ethyl-*N*-{1-[4-(propyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
19	methyl 3-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-

	pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-phenylpropanoate
20	1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
21	*N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
22	ethyl ({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)(phenyl)acetate
23	1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
24	1-ethyl-*N*-[(1*S*)-2-(methyloxy)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
25	*N*-[(1*R*)-2-amino-2-oxo-1-phenylethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
26	1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
27	1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
28	1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
29	1-ethyl-*N*-[(1*R*)-2-(methyloxy)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
30	1-ethyl-*N*-(2-hydroxy-1,1-diphenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
31	*N*-[1-(3-cyanophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
32	*N*-[cyano(phenyl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
33	*N*-{cyclopropyl[4-(methyloxy)phenyl]methyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
34	1-ethyl-*N*-[1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
35	*N*-(1,2-diphenylethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
36	1-ethyl-*N*-{1-[4-(methyloxy)phenyl]butyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
37	1-ethyl-*N*-[(1*R*)-1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
38	1-ethyl-*N*-[(1*S*)-1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
39	*N*-[1-(aminocarbonyl)-1-phenylpropyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

40	1-ethyl-*N*-(1-phenylcyclopentyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
41	1-ethyl-*N*-(4-phenyltetrahydro-2*H*-pyran-4-yl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
42	1-ethyl-*N*-(1-phenylcyclopropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
43	*N*-{1-[4-(cyclohexyloxy)-3-methylphenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
44	*N*-{1-[3-(cyclohexyloxy)-4-(methyloxy)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
45	*N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
46	*N*-{1-[4-(cyclohexyloxy)-3-hydroxyphenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
47	*N*-{1-[4-(cyclopentyloxy)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
48	1-ethyl-*N*-[1-(4-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
49	*N*-{1-[4-(1,1-dimethylethyl)phenyl]cycloheptyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
50	*N*-[1-(4-bromophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
51	1-ethyl-*N*-[(1*S*)-1-(4-iodophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
52	*N*-{1-[4-(aminosulfonyl)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
53	1-ethyl-*N*-(1-methyl-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
54	*N*-[1-(1,3-benzodioxol-5-yl)cyclohexyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
55	1-ethyl-*N*-{1-[4-(methyloxy)phenyl]cyclohexyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
56	1-ethyl-*N*-[1-(4-fluorophenyl)cyclohexyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
57	*N*-[1-(3-chlorophenyl)cyclopentyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
58	*N*-[1-(2-chlorophenyl)cyclopentyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
59	*N*-{1-[4-(1,1-dimethylethyl)phenyl]cyclohexyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

60	1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
61	*N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
62	1-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
63	1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
64	1-ethyl-*N*-{(1*S*)-1-[4-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
65	1-ethyl-*N*-(1-phenylhexyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
66	1-ethyl-*N*-(1-phenylpentyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
67	1-ethyl-*N*-(2-methyl-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
68	1-ethyl-*N*-(1-phenylbutyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
69	1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(2,2,2-trifluoro-1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
70	*N*-[cyclopropyl(phenyl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
71	1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
72	*N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
73	1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
74	1-ethyl-*N*-(1-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
75	*N*-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
76	*N*-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
77	*N*-[1-(3,4-dichlorophenyl)-2-hydroxyethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
78	1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
79	1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
80	*N*-[1-(4-bromophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-

	ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
81	1-ethyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
82	*N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
83	1-ethyl-*N*-[1-(4-methylphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
84	1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
85	1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
86	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
87	1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
88	1-ethyl-*N*-[1-(2-methylphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
89	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
90	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
91	1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
92	*N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
93	*N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
94	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
95	*N*-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
96	*N*-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
97	*N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
98	*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
99	*N*-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

100	*N*-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
101	1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
102	*N*-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
103	1-ethyl-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
104	*N*-[1-(4-bromophenyl)-2,2,2-trifluoroethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
105	1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
106	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
107	4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
108	4-(cyclohexylamino)-*N*-(diphenylmethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
109	4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
110	ethyl ({[4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)(phenyl)acetate
111	*N*-[1-(4-chlorophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
112	4-(cyclohexylamino)-1-ethyl-*N*-(1-methyl-1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
113	4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
114	*N*-[1-(4-chlorophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
115	4-(cyclohexylamino)-*N*-(1,2-diphenylethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
116	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
117	methyl 3-({[4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-phenylpropanoate
118	4-(cyclohexylamino)-1-ethyl-*N*-[1-(hydroxymethyl)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
119	4-(cyclohexylamino)-1-ethyl-*N*-(3-hydroxy-1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
120	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-1*H*-

	pyrazolo[3,4-*b*]pyridine-5-carboxamide
121	4-(cyclohexylamino)-1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
122	4-(cyclohexylamino)-1-ethyl-*N*-[1-phenyl-2-(1-pyrrolidinyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
123	4-(cyclohexylamino)-*N*-[2-(dimethylamino)-1-phenylethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
124	4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-2-(methyloxy)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
125	*N*-[(1*R*)-2-amino-2-oxo-1-phenylethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
126	4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
127	4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
128	4-(cyclohexylamino)-1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
129	4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-2-(methyloxy)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
130	4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
131	4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-1-(1-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
132	4-(cyclohexylamino)-1-ethyl-*N*-[phenyl(4-phenyl-1,3-thiazol-2-yl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
133	*N*-[cyano(phenyl)methyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
134	4-(cyclohexylamino)-1-ethyl-*N*-[1-(1-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
135	4-(cyclohexylamino)-1-ethyl-*N*-(2-hydroxy-1,1-diphenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
136	4-(cyclohexylamino)-1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
137	4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
138	4-(cyclohexylamino)-*N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
139	4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
140	4-(cyclohexylamino)-1-ethyl-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

141	*N*-[(1*R*)-1-(4-bromophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
142	4-(cyclohexylamino)-*N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
143	4-(cyclohexylamino)-1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
144	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
145	*N*-[1-(4-bromophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
146	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
147	4-(cyclohexylamino)-*N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
148	4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
149	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
150	4-(cyclohexylamino)-1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
151	4-(cyclohexylamino)-*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
152	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
153	4-(cyclohexylamino)-1-ethyl-*N*-[1-(2-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
154	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
155	4-(cyclohexylamino)-*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
156	4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
157	4-(cyclohexylamino)-*N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
158	4-(cyclohexylamino)-*N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
159	4-(cyclohexylamino)-*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
160	*N*-[1-(4-chloro-2-fluorophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
161	*N*-[1-(3-chloro-4-methylphenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-

	pyrazolo[3,4-*b*]pyridine-5-carboxamide
162	4-(cyclohexylamino)-*N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
163	4-(cyclohexylamino)-*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
164	*N*-[1-(4-chloro-2-fluorophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
165	*N*-[1-(3-chloro-4-methylphenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
166	4-(cyclohexylamino)-1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
167	*N*-[1-(4-chlorophenyl)-2-hydroxyethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
168	4-(cyclohexylamino)-*N*-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
169	4-(cyclohexylamino)-1-ethyl-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
170	4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*S*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
171	4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
172	4-[(1-acetyl-4-piperidinyl)amino]-*N*-(diphenylmethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
173	4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
174	4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
175	*N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
176	*N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
177	1-ethyl-*N*-[(1*S*)-1-(4-nitrophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
178	1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
179	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
180	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
181	1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-

	pyrazolo[3,4-*b*]pyridine-5-carboxamide
182	1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
183	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-(1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
184	(2*R*)-[({1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl}carbonyl)amino][3-(methyloxy)phenyl]ethanoic acid
185	1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
186	1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
187	*N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
188	1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
189	1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
190	*N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
191	1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
192	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
193	*N*-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
194	1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
195	*N*-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
196	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
197	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
198	1-ethyl-*N*-[1-(2-methylphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
199	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
200	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
201	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-

	(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
202	*N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
203	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
204	1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
205	*N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
206	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
207	*N*-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
208	*N*-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
209	*N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
210	*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
211	*N*-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
212	*N*-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
213	1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
214	1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
215	*N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
216	1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
217	1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
218	*N*-[1-(4-bromophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
219	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
220	*N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
221	1-ethyl-*N*-[1-(4-methylphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-

	pyrazolo[3,4-*b*]pyridine-5-carboxamide
222	1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
223	1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
224	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
225	*N*-[1-(4-bromophenyl)-2,2,2-trifluoroethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
226	1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
227	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
228	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
229	*N*-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
230	*N*-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
231	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
232	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
233	1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
234	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
235	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
236	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
237	*N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
238	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

239	1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
240	*N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
241	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
242	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
243	*N*-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
244	*N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
245	*N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
246	*N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
247	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[3-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
248	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
249	*N*-[1-(4-bromophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
250	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
251	*N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
252	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(4-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
253	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
254	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(2-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
255	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-{[4-

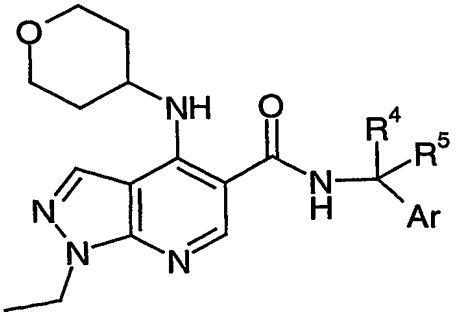
	(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
256	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
257	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(2-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
258	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
259	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
260	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
261	*N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
262	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
263	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
264	*N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
265	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
266	*N*-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
267	*N*-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
268	*N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
269	*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
270	*N*-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-{[4-

	(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
271	*N*-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
272	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(3-hydroxyphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
273	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(3-hydroxyphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
274	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
275	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
276	*N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
277	*N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
278	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
279	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
280	1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
281	1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
282	*N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
283	1-ethyl-4-{[(1*S*,3*R*)- and (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
284	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Isomer 1)
285	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

	(Isomer 2)
286	*N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
287	*N*-[1-(4-chlorophenyl)propyl]-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
288	*N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
289	*N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
290	*N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
291	*N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
292	*N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
293	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
294	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
295	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
296	*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
297	*N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
298	*N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
299	1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
300	1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
301	1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
302	1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
303	*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
304	*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-

	ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
305	1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Diastereoisomer 1)
306	1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Diastereoisomer 2)
307	*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2) hydrochloride
308	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
309	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
310	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
311	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
312	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
313	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
314	4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

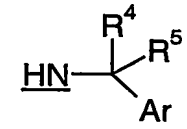
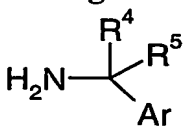
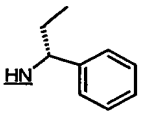
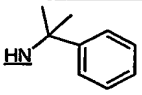
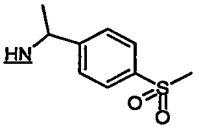
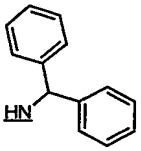
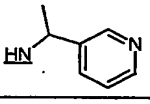
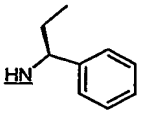
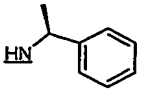
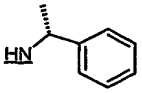
Examples 1-105

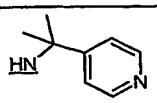
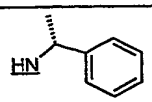
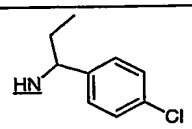
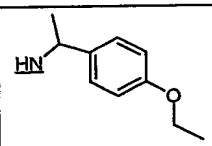
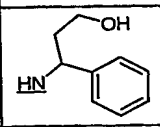
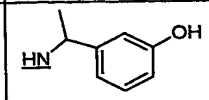
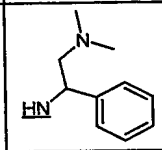
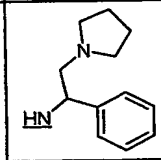
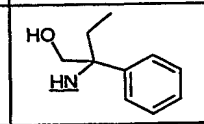
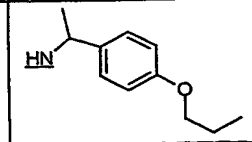
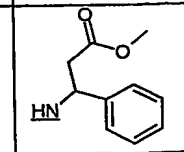
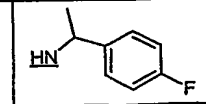
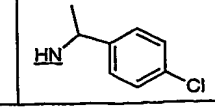


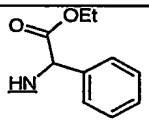
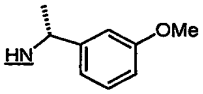
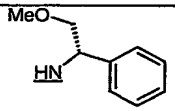
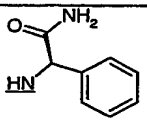
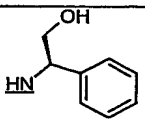
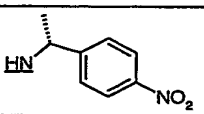
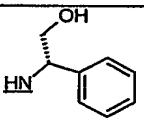
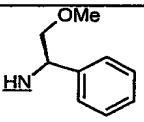
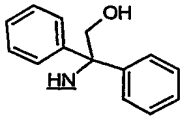
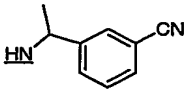
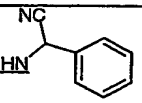
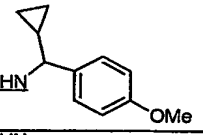
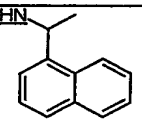
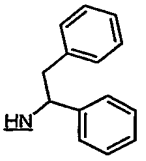
General Procedure:

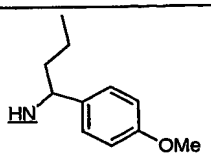
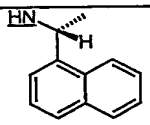
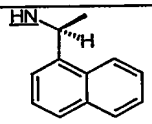
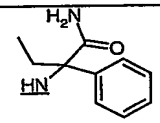
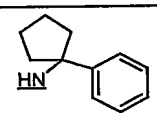
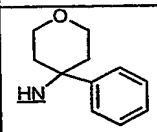
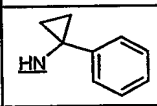
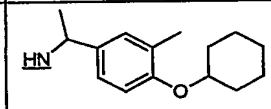
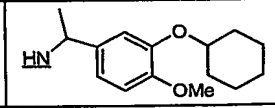
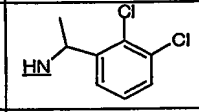
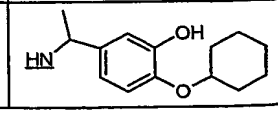
A mixture of Intermediate 13 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

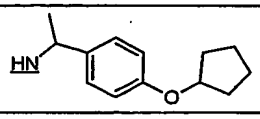
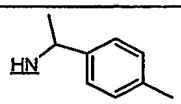
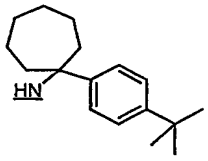
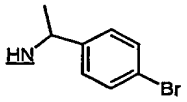
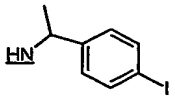
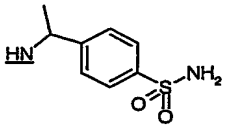
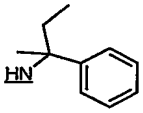
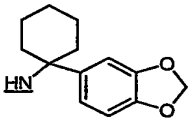
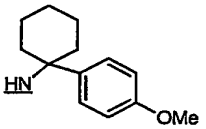
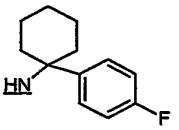
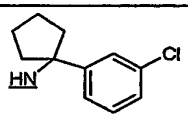
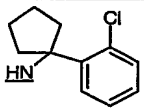
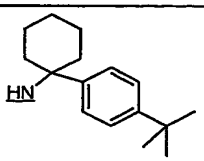
The following Examples 1-105 were prepared from Intermediate 13 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

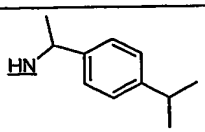
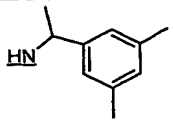
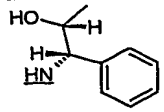
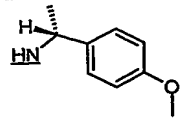
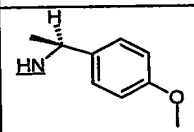
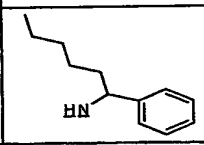
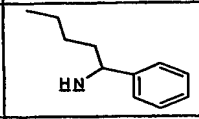
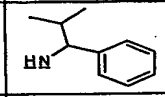
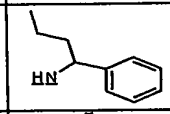
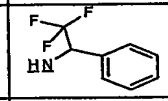
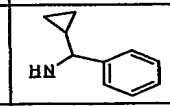
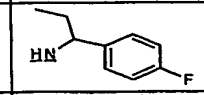
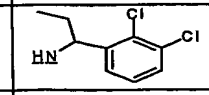
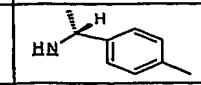
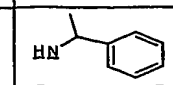
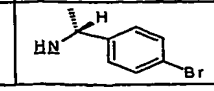
Example Number	 (connecting nitrogen underlined)	**Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
1		Lancaster	408	3.05
2		Fluorochem. Ltd.	408	2.69
3		Peakdale Molecular Ltd.	472	2.44
4		Aldrich	456	3.06
5			395	1.83
6		Lancaster	408	2.81
7		Aldrich	394	2.64
8		Aldrich	394	2.89

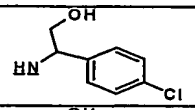
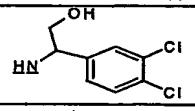
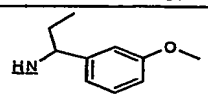
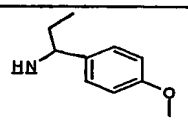
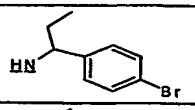
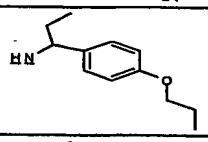
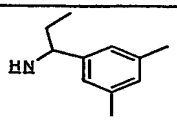
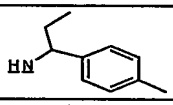
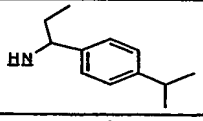
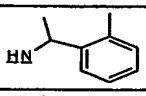
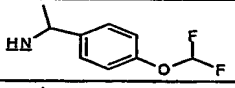
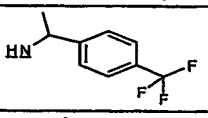
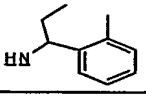
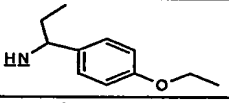
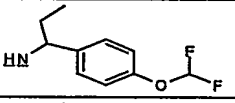
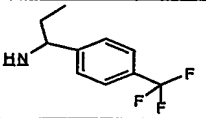
9			409	1.89
10		Aldrich	394	2.91
11		J. Pharm. Pharmacol; 1997, 49 (1), 10-15	442 + 444	3.22
12		Tim Tec Building Blocks Inc. (Intermediate 64)	438	2.98
13		Acros	424	2.71
14		Tetrahedron, 1977, 33 (5), 489-495 (Intermediate 88)	410	2.70
15		MicroChemistry Building Blocks	437	2.34
16		MicroChemistry Building Blocks	463	2.37
17		EP 534553 A1 (1993)	438	2.83
18		Biochem. Pharm. 1959, 2, 264-9 (no ref. To preparation)	452	3.22
19		Chembridge Europe	452	2.95
20		Aldrich	412	3.06
21		Bionet Research	428 + 430	3.24

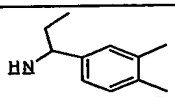
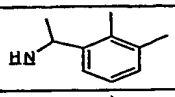
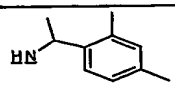
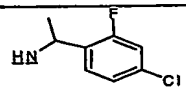
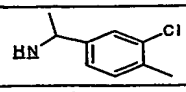
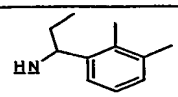
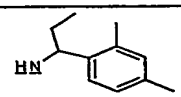
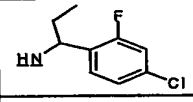
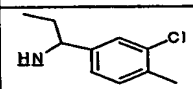
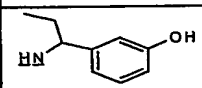
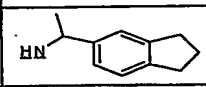
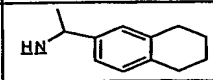
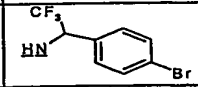
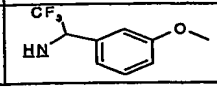
22		Maybridge Combichem.	452	3.10
23		Lancaster	424	3.01
24		Omega Chem	424	2.90
25		Acros	423	2.57
26		Aldrich	410	2.67
27		Aldrich (hydrochloride)	439	3.07
28		Aldrich	410	2.67
29		Omega Chem	424	2.90
30		Org. Lett; 2001, 3 (2), 299-302	486	3.09
31		J. Amer. Chem. Soc; 1990, 112, 5741-5747	419	2.98
32		Aldrich	405	3.06
33		Interchim Intermediates	450	3.15
34		Fluka	444	3.36
35		Aldrich	470	3.40

36		Gaodeng Xuexiao Huaxue Xuebao, 2001, 22 (10, Suppl.), 89-91	452	3.29
37		Fluka	444	3.36
38		Fluka	444	3.36
39		Tim Tec Stock Library	451	2.36
40		Synthesis, 1978, 1, 24-6.	434	2.80
41		J. Med. Chem; 1967, 10 (1), 128-9	450	2.44
42		Org. Lett; 2003, 5 (5), 753-755	406	2.99
43		Biochem. Pharmacol., 1959, 2, 264-9 (Prep. Not given)	506	3.75
44		Not known	522	3.32
45		Sigma	462 + 464	3.38
46			508	3.28

47			478	3.39
48		Aldrich	408	3.09
49			518	3.88
50		Aldrich	472 + 474	3.22
51			520	3.30
52			473	2.57
53		SALOR	422	3.12
54			491	3.26
55			478	3.30
56			466	3.31
57			468 + 470	3.38
58			468 + 470	3.22
59			504	3.74

60		Tim Tec Building Blocks B (Intermediate 90)	436	3.36
61		Intermediate 87	422	3.23
62			424	2.58
63		Lancaster	424	2.87
64		Lancaster	424	2.98
65		Intermediate 95	450	3.54
66		Intermediate 96	436	3.39
67		Intermediate 98	422	3.19
68		Intermediate 99	422	3.17
69		Intermediate 92	448	3.21
70		Intermediate 97	420	3.09
71		US 4154599 (1980)	426	3.18
72			476	3.53
73		Lancaster	408	3.14
74		Aldrich	394	2.99
75		Lancaster	472	3.28

76		Ger. Offen DE4443892 (1996)	445	2.85
77		WO 9709335 (1997)	478	2.95
78		Intermediate 72	438	3.12
79		Intermediate 73	438	3.10
80		Intermediate 74	486	3.39
81		Intermediate 77	466	3.41
82		Intermediate 85	436	3.39
83		Intermediate 75	422	3.26
84		Intermediate 80	450	3.51
85		Intermediate 63	408	3.13
86		Intermediate 65	460	3.17
87		Intermediate 66	462	3.67
88		Intermediate 70	422	3.40
89		Intermediate 76	452	3.24
90		Intermediate 78	474	3.28
91		Intermediate 79	476	3.81

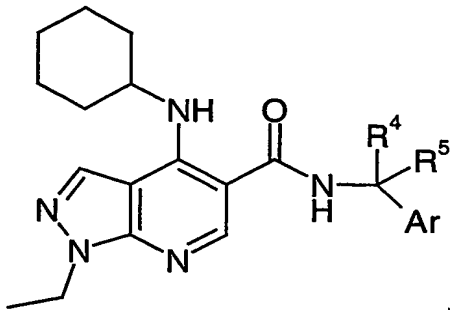
92		Intermediate 84	436	3.37
93		Intermediate 67	422	3.46
94		Intermediate 62	422	3.28
95		Intermediate 68	446	3.31
96		Intermediate 69	442	3.36
97		Intermediate 81	436	3.58
98		Intermediate 82	436	3.41
99		Intermediate 83	460	3.43
100		Intermediate 86	456	4.02
101		Intermediate 71	424	2.87
102		Intermediate 90	433	3.18
103		Intermediate 91	447	3.29
104		Intermediate 93	527	3.35
105		Intermediate 94	478	3.14

Alternative Preparation of Example 73

A solution of Intermediate 13 (2.0g) in thionyl chloride (20ml) was stirred and heated at reflux for 2.5 hours. The solution was cooled and the thionyl chloride was removed *in vacuo* to leave the intermediate acid chloride (2.1g). A solution of the acid chloride (2.1g), (R)-1-(4-methylphenyl)ethylamine (1.0g) and DIPEA (1.4g) in THF (100ml) was stirred for 18 hours. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between 0.5M sodium bicarbonate (250ml) and ethyl acetate (250ml). The organic phase was separated, washed with water (250ml), dried over Na_2SO_4 and concentrated *in vacuo* to give a foam. The foam was crystallised from a (5:1) mixture of

cyclohexane and Et_2O. One recrystallisation from a (5:1) mixture of cyclohexane and Et_2O gave Example 73 (0.96g) as white needles.
LC-MS showed $MH^+ = 408$; $T_{RET} = 3.05$ min.

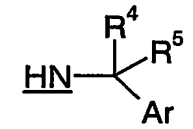
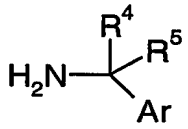
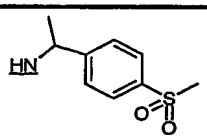
Examples 106-169

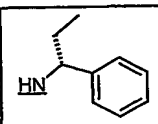
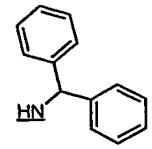
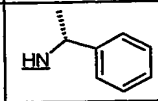
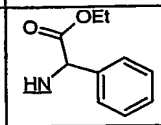
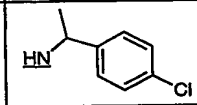
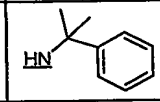
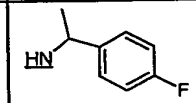
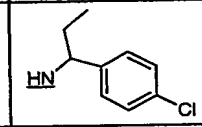
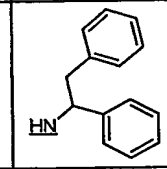
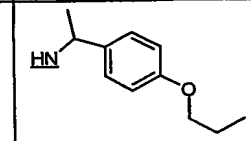
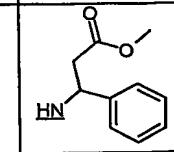
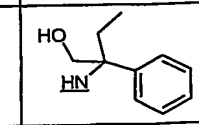
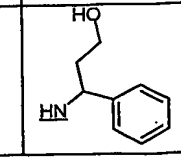


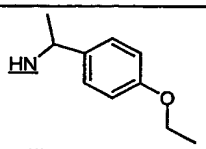
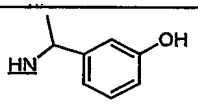
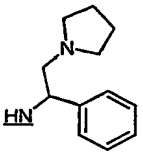
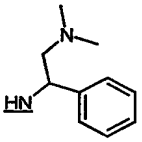
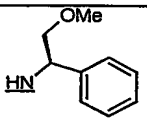
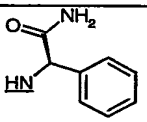
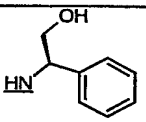
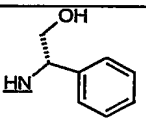
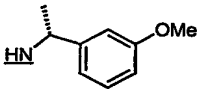
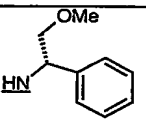
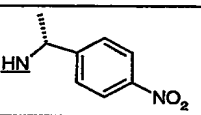
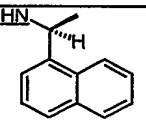
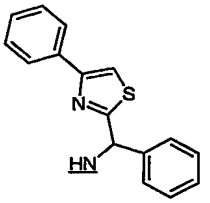
General Procedure:

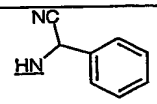
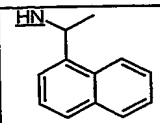
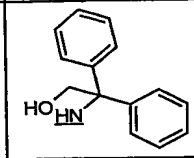
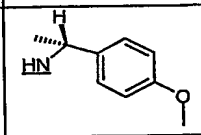
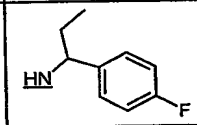
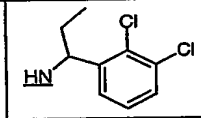
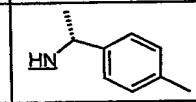
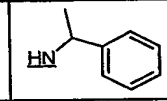
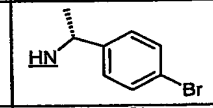
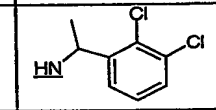
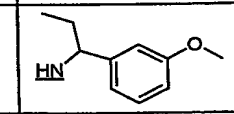
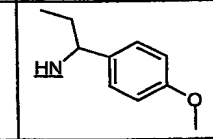
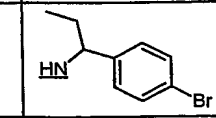
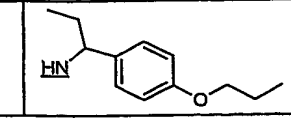
A mixture of Intermediate 14 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

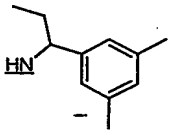
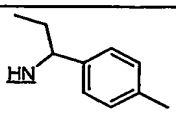
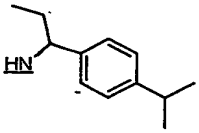
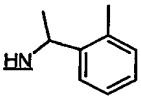
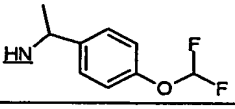
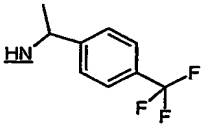
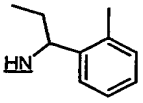
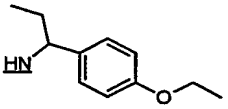
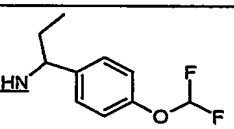
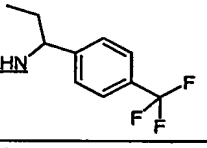
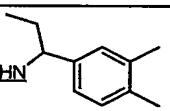
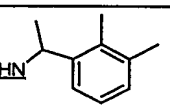
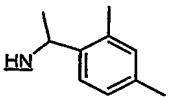
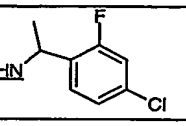
The following Examples 106-169 were prepared from Intermediate 14 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

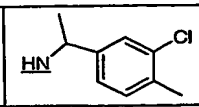
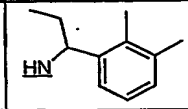
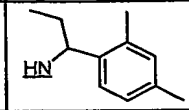
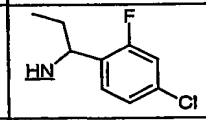
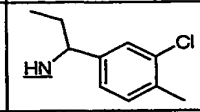
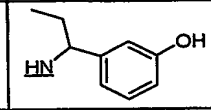
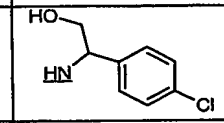
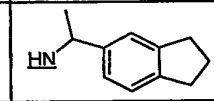
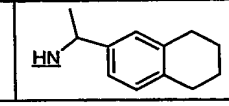
Example Number	 (connecting nitrogen underlined)	Source of amine reagent 	MH^+ Ion	LC-MS retention time
106		Peakdale Molecular Ltd.	470	3.25

107		Lancaster	406	3.72
108		Aldrich	454	3.88
109		Aldrich	392	3.60
110		Maybridge Combichem	450	3.65
111		Bionet Research	426	3.82
112		Fluorochem. Ltd.	406	3.64
113		Aldrich	410	3.64
114			440	3.93
115		Aldrich	468	3.90
116			450	3.78
117		Chembridge Europe	450	3.49
118			436	3.39
119		Acros	422	2.81

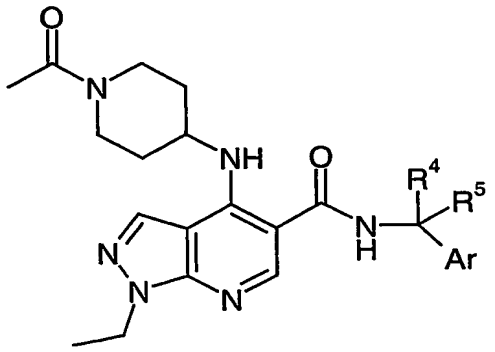
120		Tim Tec Building Blocks Inc. (Intermediate 64)	436	3.22
121		Intermediate 88	408	2.87
122		MicroChemistry Building Blocks	461	2.26
123		MicroChemistry Building Blocks	436	2.23
124		Omega Chem	422	3.47
125			421	3.08
126		Aldrich	408	3.21
127		Aldrich	408	3.21
128		Lancaster	422	4.97
129		Omega Chem	422	3.02
130		Aldrich (hydrochloride)	437	3.20
131		Fluka	442	3.45
132			537	4.01

133		Aldrich (hydrochloride)	403	3.60
134		Fluka	442	3.90
135			484	3.57
136		Lancaster	422	3.54
137		US 4154599 (1980)	424	3.75
138			474	4.13
139		Lancaster	406	3.71
140		Aldrich	392	3.58
141		Lancaster	470	3.85
142		Sigma	460	4.03
143		Intermediate 72	436	3.68
144		Intermediate 73	436	3.65
145		Intermediate 74	484	3.97
146		Intermediate 77	464	3.94

147		Intermediate 85	434	3.95
148		Intermediate 75	420	3.83
149		Intermediate 80	448	4.05
150		Intermediate 63	406	3.74
151		Intermediate 65	458	3.84
152		Intermediate 66	460	3.84
153		Intermediate 70	420	3.87
154		Intermediate 76	450	4.34
155		Intermediate 78	472	4.00
156		Intermediate 79	474	3.95
157		Intermediate 84	434	3.93
158		Intermediate 67	420	3.85
159		Intermediate 62	420	3.86
160		Intermediate 68	444	4.39

161		Intermediate 69	440	4.10
162		Intermediate 81	434	3.96
163		Intermediate 82	434	3.99
164		Intermediate 83	458	4.37
165		Intermediate 86	454	4.26
166		Intermediate 71	422	3.43
167		Ger. Offen DE4443892 (1996)	442	3.38
168		Intermediate 90	431	3.76
169		Intermediate 91	445	3.96

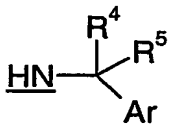
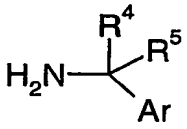
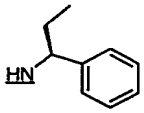
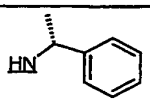
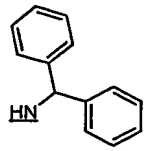
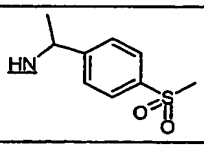
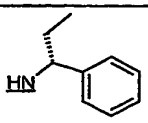
Examples 170-174



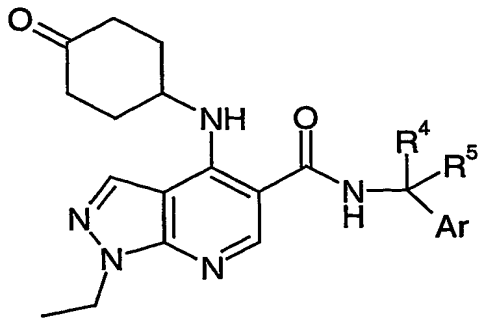
General Procedure:

A mixture of Intermediate 15 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

The following Examples 170-174 were prepared from Intermediate 15 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogen underlined)	**Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
170		Lancaster	449	2.94
171		Aldrich	435	2.84
172		Aldrich	497	3.16
173		Peakdale Molecular Ltd.	513	2.63
174		Lancaster	449	2.95

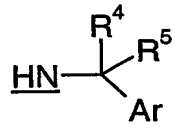
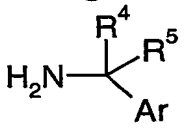
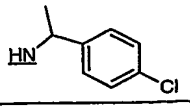
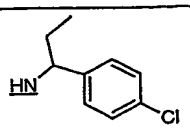
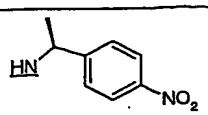
Examples 175-226

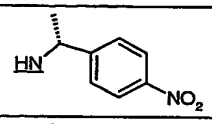
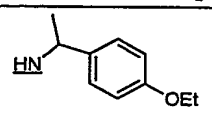
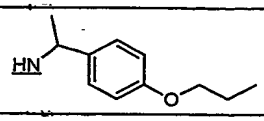
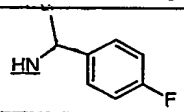
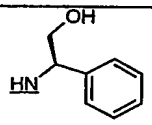
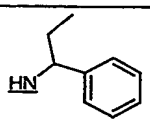
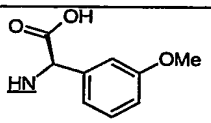
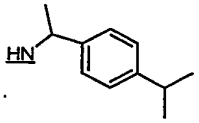
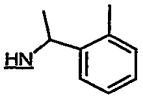
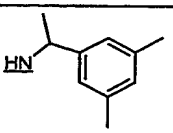
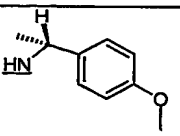
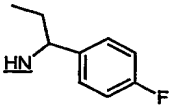
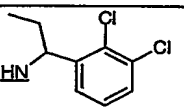
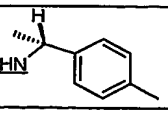


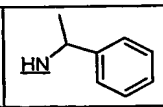
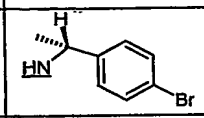
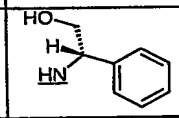
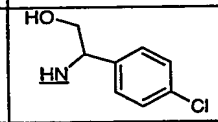
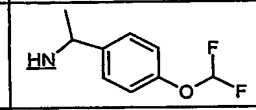
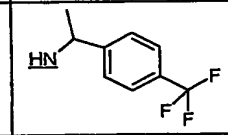
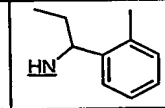
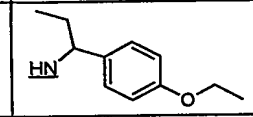
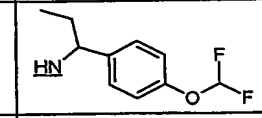
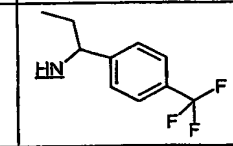
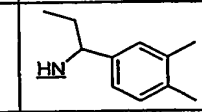
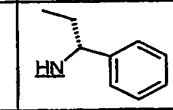
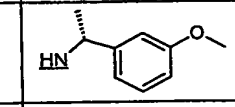
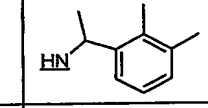
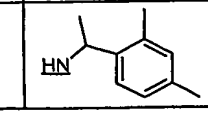
General Procedure:

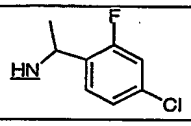
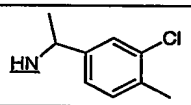
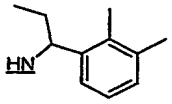
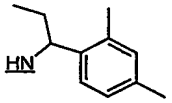
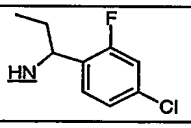
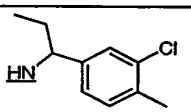
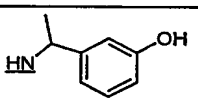
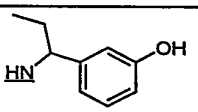
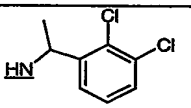
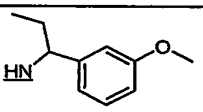
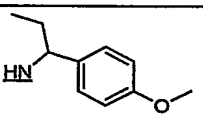
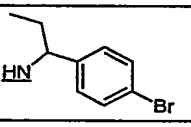
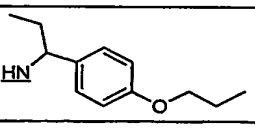
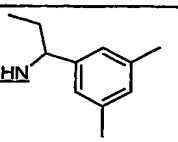
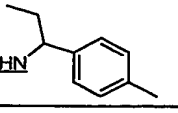
A mixture of Intermediate 16 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

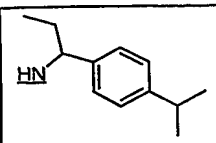
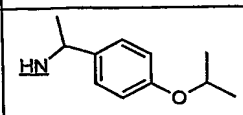
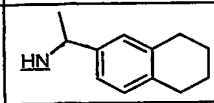
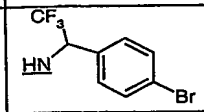
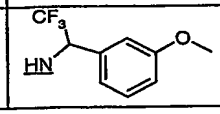
The following Examples 175-226 were prepared from Intermediate 16 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogen underlined)	Source of amine reagent 	MH^+ Ion	LC-MS retention time
175		Bionet Research	440	3.22
176			454	3.20
177		Aldrich (hydrochloride)	451	3.02

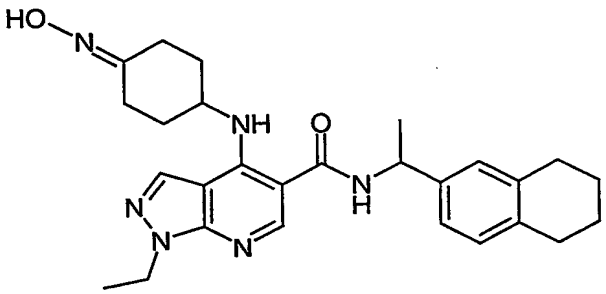
178		Aldrich (hydrochloride)	451	3.02
179		Tim Tec Building Blocks Inc. Intermediate 64	450	3.06
180		GR87015X/A	464	3.26
181		Aldrich	424	3.02
182		Aldrich	422	2.64
183		Aldrich	420	3.06
184			466	2.76
185		Tim Tec Building Blocks B Intermediate 89	448	3.36
186		Tim Tec Building Blocks B	420	2.79
187		Intermediate 87	434	3.25
188		Lancaster	436	2.99
189			438	3.19
190			488	3.52
191		Lancaster	420	3.15

192		Aldrich	406	3.01
193		Lancaster	484	3.28
194		Aldrich	422	2.54
195		Ger. Offen DE4443892 (1996)	456	2.86
196		Intermediate 65	472	2.85
197		Intermediate 66	474	3.00
198		Intermediate 70	434	2.92
199		Intermediate 76	464	2.90
200		Intermediate 78	486	2.96
201		Intermediate 79	488	3.11
202		Intermediate 84	448	3.02
203		Lancaster	420	2.79
204		Lancaster	436	2.67
205		Intermediate 67	434	2.90
206		Intermediate 62	434	2.93

207		Intermediate 68	458	2.98
208		Intermediate 69	454	3.03
209		Intermediate 81	448	3.03
210		Intermediate 82	448	3.05
211		Intermediate 83	472	3.10
212		Intermediate 86	468	3.14
213		Intermediate 88	422	2.44
214		Intermediate 71	436	2.56
215		Sigma	474	3.41
216		Intermediate 72	450	3.13
217		Intermediate 73	450	3.12
218		Intermediate 74	498	3.39
219		Intermediate 77	478	3.42
220		Intermediate 85	448	3.39
221		Intermediate 75	434	3.48

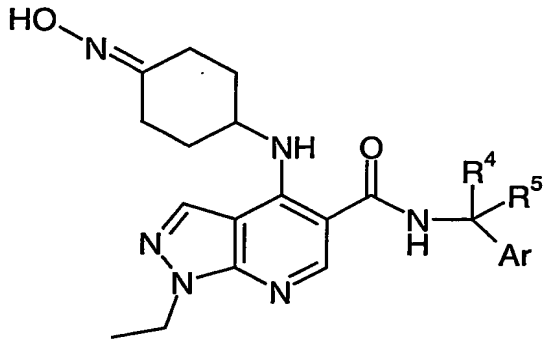
222		Intermediate 80	462	3.54
223		J. Chem. Soc. Abstracts 1951, 3430-3	464	3.19
224		Intermediate 91	460	3.39
225		Intermediate 93	539	3.45
226		Intermediate 94	490	3.24

Example 227

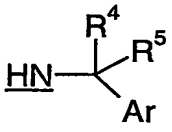
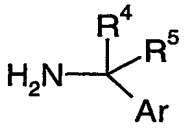
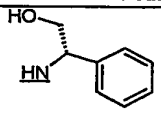
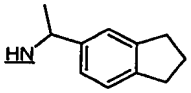
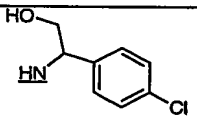


A mixture of Intermediate 17 (25mg, 0.079mmol), HATU (35mg, 0.092mmol) and DIPEA (50mg, 0.387mmol) in MeCN (2.0ml) was stirred at room temperature for 10 min. Intermediate 91 (30mg, 0.142mmol) was then added and the mixture was stirred for 2.5 hours then left to stand overnight. The solution was concentrated *in vacuo*. The residue was dissolved in EtOAc and applied to a SPE cartridge (silica, 5g). The cartridge was eluted with EtOAc. Fractions containing the desired product were concentrated *in vacuo* to give Example 227 as a white solid. LCMS showed $MH^+ = 475$; $T_{RET} = 3.32$min.

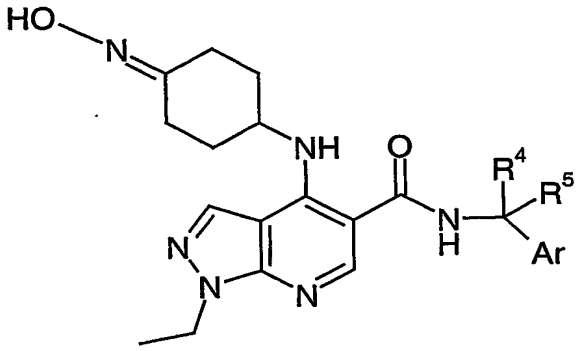
Examples 228-230



The following Examples 228-230 were prepared from Intermediate 17 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using a similar procedure to that used for the preparation of Example 227:

Example Number	 (connecting nitrogen underlined)	**Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
228		Aldrich	438	2.59
229		Intermediate 90	461	3.19
230		Ger. Offen DE4443892 (1996)	471	2.78 + 2.81

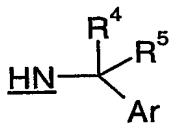
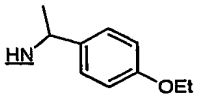
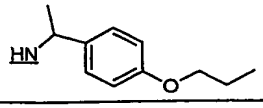
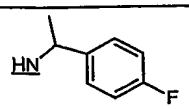
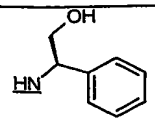
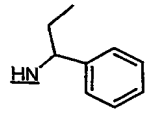
Examples 231-281

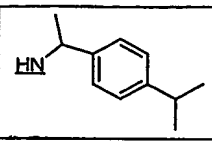
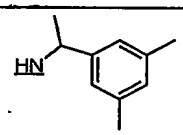
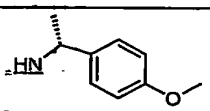
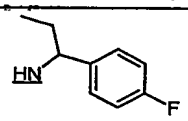
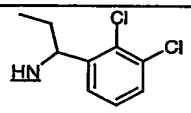
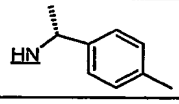
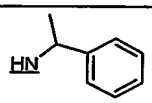
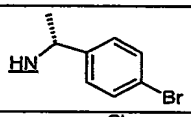
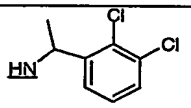
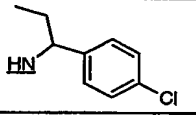
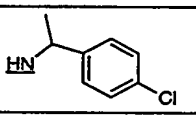
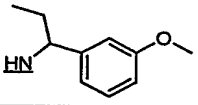
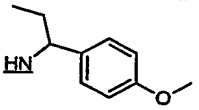
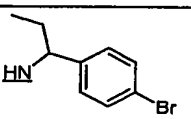
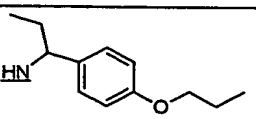


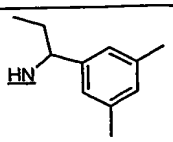
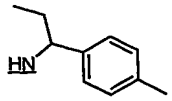
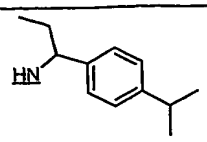
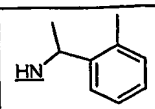
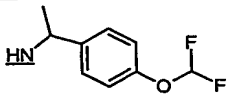
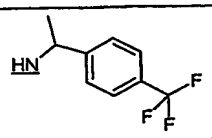
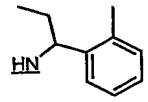
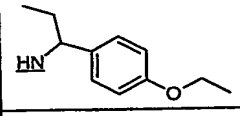
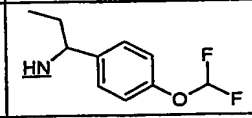
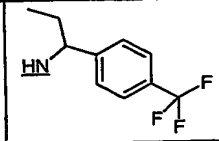
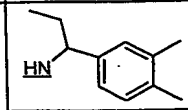
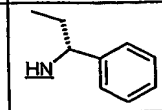
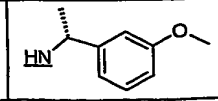
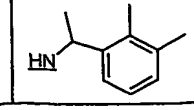
General Procedure:

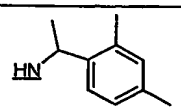
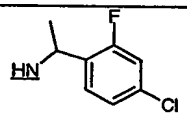
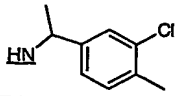
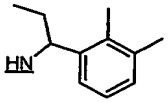
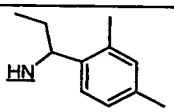
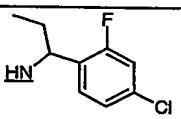
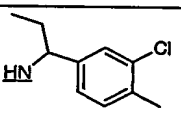
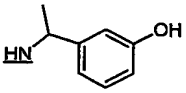
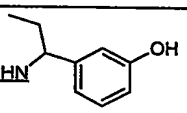
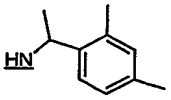
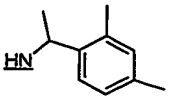
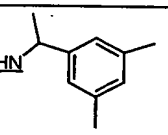
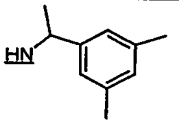
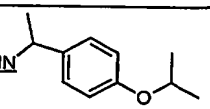
A mixture of the appropriate ketone (0.05mmol), hydroxylamine hydrochloride (0.07mmol) and DIPEA (0.05ml) in MeCN (1.0ml) was heated at reflux for 5 hours. The solvent was removed. The residue was dissolved in chloroform and applied to a SPE cartridge (silica, 0.5g). The cartridge was eluted with EtOAc. Fractions containing the desired product were concentrated *in vacuo* to give the appropriate oxime.

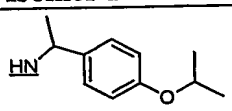
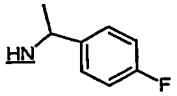
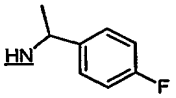
The following Examples 231-281 were prepared in this manner:

Example Number	 (connecting nitrogen underlined)	Starting Ketone	MH^+ Ion	LC-MS retention time
231		Example 179	465	2.92
232		Example 180	479	3.09
233		Example 181	439	2.87
234		Example 182	437	2.47,2.51
235		Example 183	435	3.02

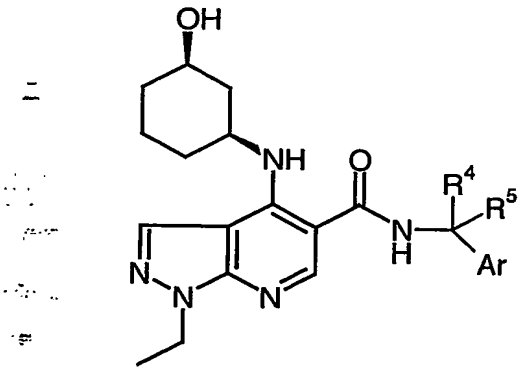
236		Example 185	463	3.28
237		Example 187	449	3.15
238		Example 188	451	2.58
239		Example 189	453	2.78
240		Example 190	503	3.11
241		Example 191	435	2.72
242		Example 192	421	2.58
243		Example 193	499	2.86
244		Example 215	489	3.01
245		Example 176	469	2.94
346		Example 175	455	2.82
247		Example 216	465	2.72
248		Example 217	465	2.70
249		Example 218	513	2.98
250		Example 219	493	2.99

251		Example 220	463	2.96
252		Example 221	449	2.84
253		Example 222	477	3.08
254		Example 186	435	2.72
255		Example 196	487	2.77
256		Example 197	489	2.92
257		Example 198	449	2.83
258		Example 199	479	2.82
259		Example 200	501	2.88
260		Example 201	503	3.02
261		Example 202	463	2.99
262		Example 203	435	2.71
263		Example 204	451	2.60
264		Example 205	449	2.82

265		Example 206	449	2.84
266		Example 207	473	2.90
267		Example 208	469	2.94
268		Example 209	463	2.93
269		Example 210	463	2.95
270		Example 211	487	3.01
271		Example 212	483	3.05
272		Example 213	437	2.40
273		Example 214	451	2.52
274	 Isomer 1	Example 295	449	3.05
275	 Isomer 2	Example 296	449	3.05
276	 Isomer 1	Example 297	449	3.06
277	 Isomer 2	Example 298	449	3.06
278		Example 299	479	3.01

	Isomer 1			
279	 Isomer 2	Example 300	479	3.01
280	 Isomer 1	Example 301	439	2.90
281	 Isomer 2	Example 302	439	2.90

Examples 282-286

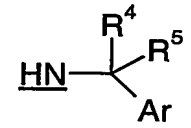
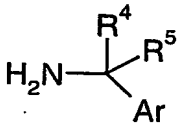
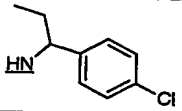
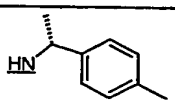
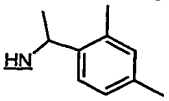


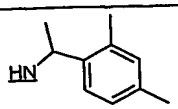
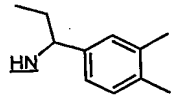
[*cis*-(3-hydroxycyclohex-1-yl)amino group; (1:1) mixture of *cis*-stereoisomers]

General Procedure:

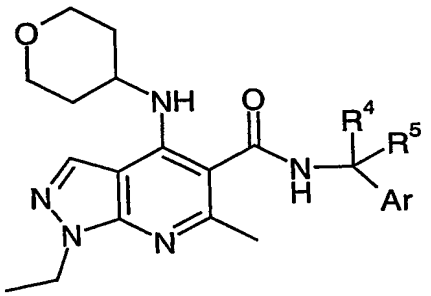
A mixture of Intermediate 19 (0.075mmol), HATU (0.09mmol) and DIPEA (0.19mmol) in MeCN (2.0ml) was stirred at room temperature for 10min. then added to the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.075mmol). The reaction mixture was stirred at room temperature for 7h. The solvent was removed by blowing nitrogen over the reaction mixture. The residue was partitioned between EtOAc (5ml) and 0.5M sodium bicarbonate (5ml). The organic phase was separated, washed with water (5ml) and dried over $MgSO_4$. The solvent was blown off and the residue dried *in vacuo* to leave the desired product.

The following Examples 282-286 were prepared from Intermediate 19 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogen underlined)	**Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
282			456	3.19
283		Lancaster	422	2.91
284	 Isomer 1	Intermediate 100	436	3.12

285	 Isomer 2	Intermediate 101	436	3.14
286		Intermediate 84	450	3.15

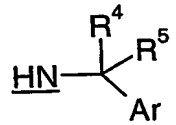
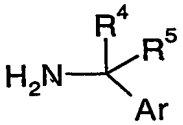
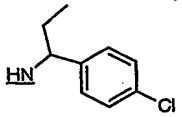
Examples 287-288

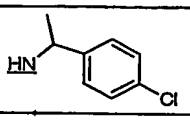


General Procedure:

A mixture of Intermediate 18 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

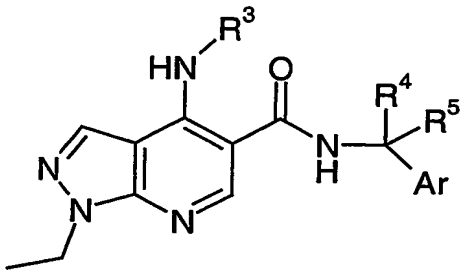
The following Examples 287-288 were prepared from Intermediate 18 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogens underlined)	**Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
287			456 + 458	2.88

288		Bionet Research	442 + 444	2.73

Examples 289-306

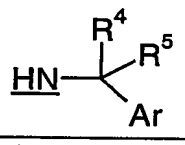
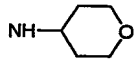
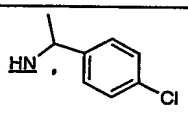
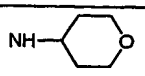
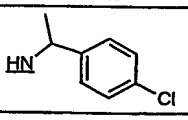
Separation of isomers of Examples on Chiral Columns

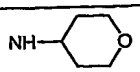
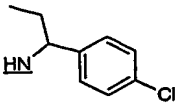
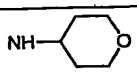
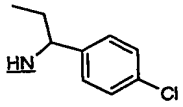
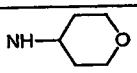
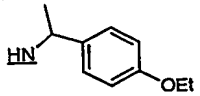
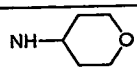
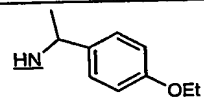
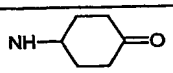
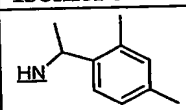
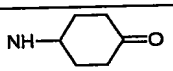
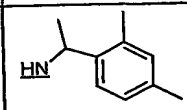
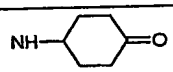
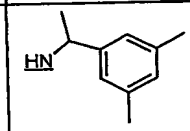
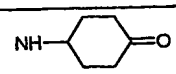
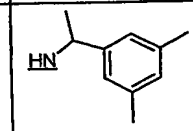
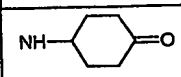
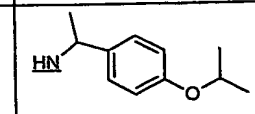
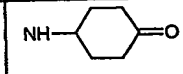
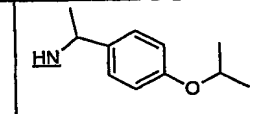
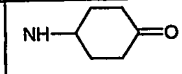
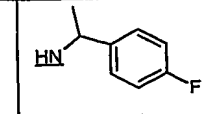


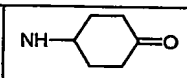
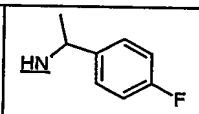
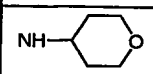
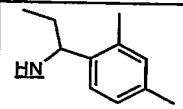
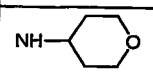
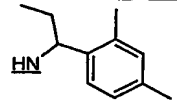
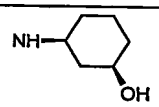
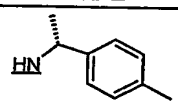
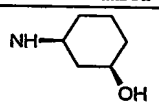
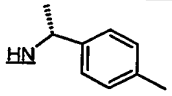
General Procedure:

Racemic Examples were resolved by preparative chiral column chromatography, using either a 2-inch x 20cm Whelk 0-1 chiral column with 100% EtOH or a mixture of EtOH and n-heptane as the eluent or a 2-inch Chiralpak AD chiral column with 100% ethanol as the eluent. In the Table, "Isomer 1" relates to the first enantiomer to be eluted from the column and "Isomer 2" relates to the second enantiomer.

Example 283 (mixture of diastereoisomers) was also separated into its component isomers by preparative chiral column chromatography, using a 2-inch Chiralcel OD chiral column with a (95:5) mixture of heptane and ethanol as the eluent. In the Table, "Isomer 1" relates to the first enantiomer to be eluted from the column and "Isomer 2" relates to the second enantiomer.

Example Number	**NHR^3**		**Starting Material**	**MH$^+$ Ion**	**LC-MS retention time**
289		 Isomer 1	Example 21	428	3.18
290			Example 21	428	3.18

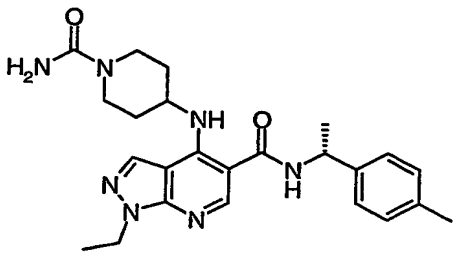
		Isomer 2			
291		 Isomer 1	Example 11	442	3.30
292		 Isomer 2	Example 11	442	3.30
293		 Isomer 1	Example 12	438	3.07
294		 Isomer 2	Example 12	438	3.07
295		 Isomer 1	Example 206	434	3.25
296		 Isomer 2	Example 206	434	3.25
297		 Isomer 1	Example 187	434	3.25
298		 Isomer 2	Example 187	434	3.26
299		 Isomer 1	Example 223	464	3.21
300		 Isomer 2	Example 223	464	3.19
301		 Isomer 1	Example 181	424	2.93

302		 Isomer 2	Example 181	424	2.93
303		 Isomer 1	Example 98	436	3.36
304		 Isomer 2	Example 98	436	3.36
305	 *Cis* Isomer 1		Example 283	422	2.90
306	 *Cis* Isomer 2		Example 283	422	2.90

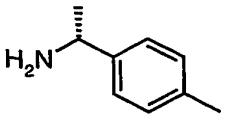
Example 307 Preparation of the Hydrochloride of Example 304

A solution of Example 304 (1.3g) in Et_2O (30ml) was treated, rapidly dropwise with stirring, with a molar excess (relative to Example 304) of 1.0M hydrogen chloride in Et_2O. The resultant suspension was left to stand for 2 hours. The solvent was removed *in vacuo*. The residual solid was recrystallised from ethanol to give the hydrochloride (0.64g) as white needles. LC-MS showed $MH^+ = 436$; $T_{RET} = 3.35$ min.

Example 308: 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

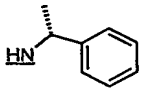
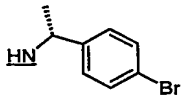
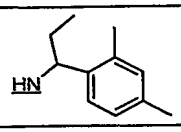
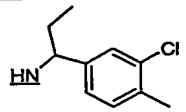
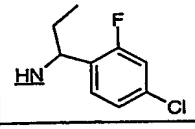


A solution of Intermediate 105 (0.066mmol) in DMF (1ml) was treated with EDC (0.066mmol), HOBT (0.066mmol) and DIPEA (0.151mmol) followed by

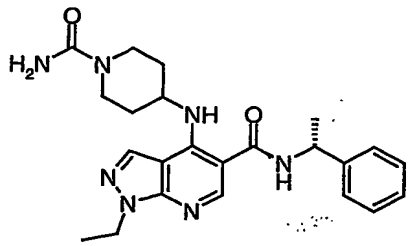


(0.066mmol). The reaction mixture was left to stand at 22°C for 16h. The DMF was evaporated and the residue was partitioned between DCM (5ml) and saturated aqueous sodium bicarbonate (2ml). The organic layer was collected through a hydrophobic frit and evaporated. The residue was purified by mass directed autoprep. HPLC to give the title compound as a gum (8.9mg). LCMS showed $MH^+ = 450$; $T_{RET} = 2.76$min.

The following Examples 309-313 were prepared from Intermediate 105 and the appropriate amine HNR^4R^5 using this procedure:

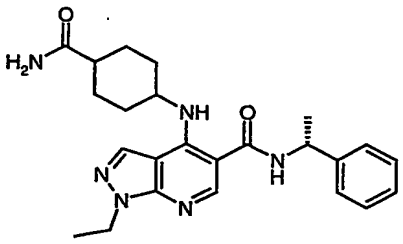
Example Number	NR^4R^5	Source of amine reagent	MH^+ Ion	LC-MS retention time
309		Aldrich	436	2.62
310		Lancaster	516	2.8
311		Intermediate 82	478	2.96
312		Intermediate 86	498	2.9
313		Intermediate 83	502	2.88

<u>Alternative Preparation of Example 309:</u> 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



A mixture of Intermediate 109 (27mg) and Intermediate 111 (16mg) in MeCN (2ml) was treated with DIPEA (35μL). The reaction mixture was heated under reflux for 72h. The solvent was evaporated and the residue was partitioned between DCM (5ml) and saturated aqueous sodium bicarbonate (2ml). The organic layer was collected through a hydrophobic frit and evaporated. The residue was purified by mass directed autoprep. HPLC to give Example 309 as a white solid (5.0mg). LCMS showed $MH^+ = 436$; $T_{RET} =$ 2.62min.

Example 314: 4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



A solution of intermediate 109 (0.08mmol) in MeCN (1ml) was treated with intermediate 114 or 113 (0.088mmol) and DIPEA (0.2mmol). The reaction mixture was heated at reflux for 20h. The solvents were evaporated and the residue was partitioned between DCM (5ml) and water (2ml). The organic phase was collected through a hydrophobic frit and evaporated. The residue was purified by mass directed autoprep. HPLC to give Example 314 as a white solid (12.2mg). LCMS showed $MH^+ = 435$; $T_{RET} = 2.7$min.